Archives of Neurology and Psychiatry

VOLUME 41 JANUARY 1939 NUMBER 1

SOMNOLENCE CAUSED BY HYPOTHALAMIC LESIONS IN THE MONKEY

S. W. RANSON, M.D.
CHICAGO

Lesions have been placed in the diencephalon in 55 monkeys, and these animals have been observed for abnormalities in their reactions. A few monkeys died within a short time after the operation, and in others the lesions were not properly placed. Elimination of these unsatisfactory experiments leaves 35 animals from which valid information can be drawn. Since there are reasons for believing that either side of the hypothalamus is capable of activating structures on both sides of the body, it was necessary that the lesions should be at least approximately bilaterally symmetric. The 35 satisfactory experiments may be divided into the following groups: 11 in which the lesions involved both lateral hypothalamic areas to the level of the caudal border of the mamillary bodies; 6 in which the lesions in the lateral hypothalamic areas did not extend back beyond the rostral border of the mamillary bodies; 9 in which the laterally placed lesions did not reach far enough ventrally to involve the lateral hypothalamic areas; 2 in which the lesions were placed medially and 7 in which the lesions were in the thalamus. Dr. W. R. Ingram placed the lesions in the hypothalamus and made some of the observations on these animals. Dr. H. W. Magoun made the lesions in the thalamus.

METHODS

Young rhesus monkeys (Macaca mulatta), weighing from 3 to 6 pounds (1.5 to 2.5 Kg.), were used. The lesions were made with the aid of the Horsley-Clarke stereotaxic instrument. The operations were performed with the animals under anesthesia induced with pentobarbital sodium and were usually completed about noon. During the afternoon the monkeys were kept warm with a heating pad to combat the drop in temperature caused by the anesthesia and the tendency to hypothermia caused by lesions in the caudal part of the hypothalamus. If at the end of the afternoon the temperature fell when the heating pad was removed the animals were placed in an incubator for the night, and as much longer as proved necessary. When monkeys anesthetized in the morning are kept warm the hypnotic effect of pentobarbital sodium completely disappears before the next morning.

From the Institute of Neurology, Northwestern University Medical School.

Aided by grants from the Rockefeller Foundation and the Ella Sachs Plotz Foundation.

For the lesions in the hypothalamus a unipolar electrode was used, with the indifferent electrode in the rectum. For the larger lesions in the thalamus a bipolar, needle-like electrode, with the tips of the constituent wires separated by 3 mm. along the long axis of the needle, was employed. The bipolar electrodes did not exceed 1 mm. in diameter, and the unipolar electrodes were even more slender. The construction of the electrodes and other points concerning the technic have been discussed elsewhere (Ranson,[1] Harrison[2]). To destroy as completely as possible the lateral hypothalamic area on both sides of the brain, the electrode was inserted successively 2.5 mm. to the right and left of the midline along the frontal plane 7 mm. rostral to the interaural line; three lesions were made along each puncture at 1, 2.2 and 3.5 mm. below the zero horizontal plane. This was then repeated at the frontal plane 8 mm. rostral to the interaural line. Thus, there were two punctures 1 mm. apart on each side of the brain, and along each puncture there were three lesions. Each lesion was made by a current of 3 milliamperes flowing for sixty seconds and was large enough that the six lesions on each side fused into a single one about 4 mm. long. The obliquity of the brain stem with reference to the head is such that the long axis of the lesion coincided closely with the long axis of the lateral hypothalamic area.

RESULTS

Bilateral lesions in the lateral hypothalamic areas extending to the level of the caudal border of the mamillary bodies have been most effective in producing somnolence. Two examples will now be given.

Monkey 20.—This animal had a subnormal temperature and was kept in the incubator for a number of days after the operation. On the thirty-fourth day after operation the rectal temperature was 97 F., or 4 degrees below normal, which for the monkey is 101 F. The room temperature on that day was 77 F.

Sleep.—The morning after the operation the monkey was found sound asleep; it woke when handled and then quickly fell asleep again. This deep somnolence continued for seven days. From the eighth to the twelfth day the monkey became progressively less sleepy, but even on the forty-seventh day it remained somewhat drowsy. On this day the animal was brought to the office and was under observation for several hours. At first it was alert and interested in the new surroundings, but after about an hour it became drowsy and would sit for a long time in one position with the eyes closed. Any noise in the room caused the eyes to open, but they soon closed again. If pulled around by the chain the monkey became lively and excited, but when left alone it soon relapsed into an immobile, drowsy state. Little attention was paid to people walking through the room. When photographed with the aid of a flashlight bulb, the monkey opened its eyes but did not change its position, and the eyes soon closed again. Figure 1 *A* shows the fourth of a series of such photographs, taken a few minutes apart. The strange noise and sudden illumination accompanying the taking of the three preceding photographs had not excited the animal enough to prevent it from falling asleep promptly. Even on the sixty-fourth day there were still evidences of drowsiness. The somnolence was not directly related to the hypothermia, for on the third, fourth and sixth days, when the drowsiness was most marked, the monkey was kept in the incubator and had a normal rectal temperature.

1. Ranson, S. W.: On the Use of the Horsley-Clarke Stereotaxic Instrument, Psychiat. en neurol. bl. **[38]**:534, 1934.

2. Harrison, F.: Modifications in the Technic for the Use of the Horsley-Clarke Stereotaxic Instrument, Arch. Neurol. & Psychiat. **40**:563 (Sept.) 1938.

Emotional Reactions.—These were greatly decreased. The monkey, which before the operation had behaved like the usual recently imported rhesus, became tame and unafraid. The face remained immobile and masklike (as in fig. 1 *B*) There was none of the play of emotional expression so characteristic of the face of the normal wild monkey. When grasped by the neck and when being fed by tube the monkey struggled violently. On the twelfth and on subsequent days the monkey occasionally showed signs of fright, but not to the same extent as a normal animal. On the thirty-first day the following notation was made: "Monkey is not much afraid. Will come to the front of the cage and can be petted around the head. Objects to being caught and to being grasped about the neck. When pulled around by the collar and chain is aggressive, climbs up the chain and tries to bite." The behavior of the monkey on the day on which its photograph was taken, the forty-seventh postoperative day, has been described and was indicative of subnormal emotional response.

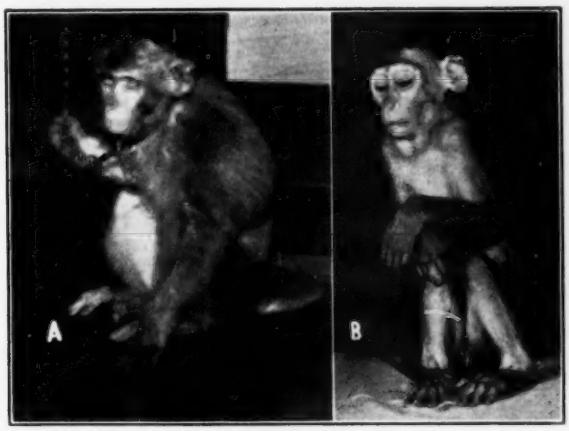


Fig. 1.—*A*, photograph of monkey 20, forty-seven days after the operation, sleeping during the last of a series of four flashlight exposures, none of which caused excitement. *B*, monkey 39 on the third day after operation. The animal was drowsy, with the eyelids drooping and the face relaxed and expressionless.

Motility.—Activity was greatly reduced and slowed. Motor initiative was lacking. On the first day there was a slight tendency to fall to the right. On the second there was excellent motor control, so that the monkey could walk along the upper edge of a 1 inch (2.5 cm.) board placed edge up. When dropped about 3 feet (1 meter) to the floor, the monkey landed on its feet and ran off normally except for slowness and a tendency to lean to the right. The lack of motor initiative persisted for many days and was clearly in evidence on the forty-seventh day, although the monkey could, when activated, run, jump and climb in a normal manner, except that the movements did not have the extreme rapidity characteristic of those of the normal monkey.

The grasp reflex was well developed during the first six days after operation, but was not recorded subsequently. On the third day the monkey could be raised from the table by a rod grasped by its two hands. When the body was raised so that the feet hung free from the table, the legs would swing up and the feet

grasp the rod. If the legs were restrained from swinging up for a few moments, the monkey gradually relaxed, hanging at full length by the arms with the eyes closed, apparently asleep (as in fig. 2).

Because of the lack of motor initiative, the monkey occasionally remained in odd postures for a time, but well defined catalepsy, resembling that observed in the cat,[3] was not seen. When the monkey was suspended in a hammock, ventral side down, the legs, hanging through holes in the hammock, offered no resistance to passive flexion. There was no support reflex (*Stütz*). When the monkey was placed back down in a trough, the limbs were flexed and did not show increase in tonus. A hand resting on the animal could occasionally feel sudden transient contractions of the skeletal musculature. Apparently, these involved the trunk muscles, but the exact muscles which contracted in these myoclonic jerks were not determined; it is possible that the limb muscles may have been involved. No tremor was seen. The deep reflexes were not tested.

Fig. 2.—Photograph of monkey 4 on the eighth day after operation, illustrating the strong grasp reflex in the hands, which enabled the animal to hang from a rod while asleep.

Gastrointestinal Tract.—Anorexia was a prominent symptom. The animal could occasionally be coaxed to take a bite of banana, but usually refused all food and had to be fed by tube for thirty-one days, by which time it had begun to eat spontaneously. It should be emphasized that there was no infection and no other obvious cause of anorexia except the hypothalamic lesions. There was no vomiting or diarrhea. The animal was killed on the sixty-eighth day. Autopsy revealed no pathologic changes in the thoracic or abdominal viscera.

Lesions in the Brain of Monkey 20 (fig. 3).—The internal capsule, basis pedunculi and medial lemniscus were bilaterally intact. There was considerable damage in the anterior part of the dorsal thalamus. The anterior group of nuclei was intact on the right but damaged on the left. The pars anterior of the ventral thalamic nucleus and the fibers of the anterior thalamic radiation were damaged

3. Ingram, W. R.; Barris, R. W., and Ranson, S. W.: Catalepsy: An Experimental Study, Arch. Neurol. & Psychiat. **35**:1175 (June) 1936.

on both sides, most extensively on the left. In the nucleus medialis dorsalis and nucleus reuniens anterior the nerve cells were largely replaced by glia. The rostral group of hypothalamic nuclei (nucleus filiformis, nucleus supraopticus, nucleus ovoideus and nucleus hypothalamicus anterior) were intact. The nucleus hypothalamicus ventromedialis was intact rostrally, but the caudal part showed glial proliferation, as did also the nucleus tuberis lateralis and the nucleus hypothalamicus posterior. The nuclei in the lateral hypothalamic area (nucleus hypo-

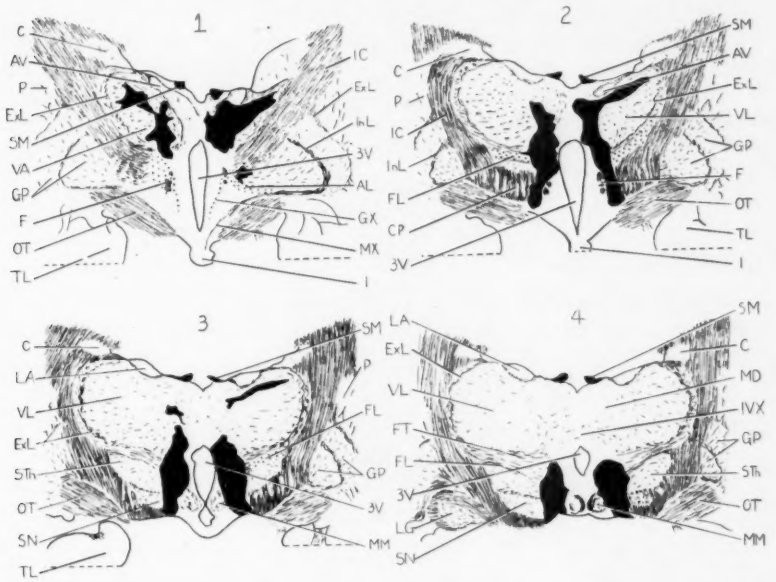


Fig. 3.—Drawings of sections through the brain of monkey 20. In this figure and in the accompanying figures, the lesions are indicated by solid black, and degenerated fiber bundles, by coarse stippling.

In this figure and in the accompanying figures, the following abbreviations are used: *AC* indicates anterior commissure; *AL*, the ansa lenticularis; *APS*, the anterior perforated substance; *AV*, the nucleus anteroventralis; *C*, the caudate nucleus; *CP*, the cerebral peduncle; *ExL*, the external medullary lamina; *F*, the fornix; *FL*, the fasciculus lenticularis (H_2); *FT*, the fasciculus thalamicus (H_1); *GP*, the globus pallidus; *GX*, Ganser's commissure; *H*, field H of Forel; H_1, field H_1 of Forel (fasciculus thalamicus); H_2, field H_2 of Forel (fasciculus lenticularis); *HP*, the habenulopeduncular tract; *I*, the infundibulum; *IC*, the internal capsule; *ITP*, the inferior thalamic peduncle; *IVX*, the interventral commissure; *InL*, the internal medullary lamina; *LA*, the nucleus lateralis, pars anterior, of the thalamus; *LG*, the lateral geniculate nucleus; *LV*, the lateral ventricle; *MD*, the nucleus medialis dorsalis of the thalamus; *ME*, the medial eminence; *MFB*, the medial bundle of the forebrain; *MM*, the medial mamillary nucleus; *MT*, the mamillothalamic tract; *MX*, Meynert's commissure; *OC*, the optic chiasm; *OT*, the optic tract; *P*, the putamen; *PB*, the pallidofugal bundle; *RN*, the red nucleus; *SM*, the stria medullaris; *SMX*, the supramamillary decussation; *SN*, the substantia nigra; *SP*, the septum pellucidum; *STh*, the subthalamic nucleus; *TL*, the temporal lobe; *Tub*, the tuber cinereum; *VA*, the nucleus ventralis, pars anterior, of the thalamus; *VL*, nucleus ventralis, pars lateralis, of the thalamus; *ZI*, the zona incerta; *3V*, the third ventricle, and *IIIN*, the third nerve.

thalamicus lateralis and nucleus ansae lenticularis) were destroyed on both sides caudal to the level of the infundibulum. More rostrally they were overgrown with glia. The mamillary nuclei (medialis, lateralis and intercalatus) showed a loss of nerve cells and proliferation of neuroglia which made it difficult to determine their outlines. The fornix was interrupted on the right side and badly damaged on the left; the mamillothalamic tract was interrupted bilaterally, as was also the supramamillary commissure and mamillary peduncle. The habenulopeduncular tract was intact on both sides. There was slight damage to the subthalamic nucleus of Luys and the substantia nigra bilaterally. The globus pallidus was not directly injured on either side, but most of its large cells had disappeared, without much increase in glia nuclei. More of the large cells were preserved in its lateral than in its medial segments. The ansa lenticularis and the large part of the fasciculus lenticularis which joins the ansa were interrupted and degenerated bilaterally. Field H of Forel was destroyed in its rostral part, but was intact immediately above the red nucleus. The red nucleus itself was intact.

Since there was no injury to the internal capsule or basis pedunculi, the slight weakness, seen in the right limbs during the first few days after the operation, can best be explained by the damage to field H of Forel.

The somnolence exhibited by monkey 20 and others of this series resembled normal sleep in that the animal could be wakened. The condition was not coma. The ease with which the animal could be wakened depended on the depth of the somnolence, which was greatest during the first few days after operation. At this time opening the door of the cage was not sufficient. It was necessary to handle or even shake the monkey, as one would a sleepy child, to waken it. Later the sleep was much less deep, and the animal wakened at the slightest noise.

In attempting to explain the somnolence in this monkey attention should be given to : (1) the lesions in the anterior part of the thalamus and destruction of the fibers belonging to the anterior thalamic radiation; (2) the degeneration of the mamillary nuclei and the interruption of the mamillothalamic tracts, and (3) the bilateral destruction of the lateral hypothalamic area. After the results obtained in other experiments have been presented, it will be possible to assess the importance of each factor. It does not seem probable that the damage to the pallidofugal fibers and the resulting disappearance of large cells in the globus pallidus could have been directly related to the somnolence. Possibly it may have been responsible for the loss of motor initiative, and the resulting quiet would then have favored sleep.

The next monkey to be considered showed similar symptoms, although the thalamus was practically intact.

Monkey 25.—This animal had a subnormal temperature during the first seven days after operation although it was kept in an incubator, and it was unable to maintain a normal temperature when kept in a comfortably warm room (from 70 to 72 F.) thirty-eight days after the operation.

Sleep.—The monkey was somnolent for five days after the operation. Thereafter, it sometimes appeared to be alert when first approached, but when it was observed for some time signs of drowsiness appeared. A note made on the fifth

day reads: "8 a. m.: Sound asleep. When the cage door was opened, the monkey raised its head and opened its eyes, blinked a few times and went off to sleep again." A note made forty-nine days after the operation reads: "3 p. m.: Has been on a chain in the office since 10 a. m., i. e., five hours. At first the monkey was alert, but has become increasingly drowsy. Is now sitting with the eyes closed and the head bowed. Has been seen to yawn. Looks and acts very sleepy, but can be easily aroused."

Emotional Reactions.—For eight days following the operation the monkey was tame, entirely unafraid and easily handled. The face had a fixed, sad expression, which did not change. The monkey did not chatter or bark. When lifted from the cage to a table, the animal did not try to get away or to bite, but it became excited and struggled when grasped about the neck. On the twenty-first day it showed timidity and retreated to the rear of the cage. The following note was made seventy-eight days after the operation: "Monkey has been handled very little during the last month, but remains unafraid and easily handled. Will come to the front of the cage and stick its head out close to one's face and allows itself to be petted. The face remains blank and emotionless, unless the animal is grasped around the neck. Does not like to be held tight and will then make grimaces, but almost never chatters or barks."

Motility.—There were loss of motor initiative and slowness of movement, but no other impairment of motor control. The monkey could walk, jump and climb. It would remain in one place, without changing its position, for a considerable period. On the fifth day the cage was left with the door open and unguarded, and the animal was watched for five minutes. Except for opening and closing its eyes, the monkey hardly moved. Once it shifted its head a little. Beginning with the seventh day activity increased, but thirty days after the operation the movements still were slower than normal.

The grasp reflex was well developed, and during the first few days after the operation the animal would hang in the air supported from a rod by its arms. When the monkey was supported, ventral side down, in a hammock with the limbs hanging free, there was not evident any increase in extensor tonus. No steady resistance was offered to manipulation of the forelegs or hindlegs. There was no myoclonic jerking of the trunk muscles, but occasionally one saw twitching of the right side of the face, consisting chiefly of elevation of the right side of the upper lip associated with winking of both eyes.

Gastrointestinal Symptoms.—The monkey ate fairly well on the first day after operation, but required tube feeding from the second to the eighth day, inclusive. It vomited once after tube feeding, but had no diarrhea. After the first month it was occasionally seen to eat feces and drink urine, although abundant food and water were available.

Lesions in the Brain of Monkey 25.—The internal capsule, basis pedunculi and medial lemniscus were intact bilaterally. The thalamus was intact except for the scars where the electrodes were inserted and for a slight extension of the lesions into the ventral part of the ventral nucleus (fig. 4). The pars anterior of the ventral nucleus and the anterior thalamic radiation were intact bilaterally. The slight damage in the thalamus was, therefore, differently located than were the thalamic lesions in monkey 20. The rostral group of hypothalamic nuclei (nucleus filiformis, nucleus supraopticus, nucleus ovoideus, nucleus hypothalamicus anterior and nucleus hypothalamicus ventromedialis) were intact. The nucleus tuberis lateralis on the right side and the nucleus hypothalamicus posterior on both sides were destroyed. The nuclei of the lateral hypothalamic area (nucleus

ansae lenticularis and nucleus hypothalamicus lateralis) were destroyed bilaterally at the level of the mamillary bodies and for some distance more rostrally. All the nuclei of the mamillary bodies were destroyed by the lesions or were replaced by glia, so that their margins could scarcely be recognized. The fornix, mamillothalamic tract, supramamillary commissure and mamillary peduncle were destroyed bilaterally. The habenulopeduncular tract was intact. The descending bundle of pallidofugal fibers formed by the junction of the ansa lenticularis and the larger part of the fasciculus lenticularis was interrupted bilaterally. Rostral to the lesion the ansa suffered retrograde degeneration. Many of the large cells of the globus pallidus had disappeared. The substantia nigra and the subthalamic nucleus were intact on the right, but on the left side their medial borders were damaged. Field H of Forel, where it lies immediately rostral to the red nucleus,

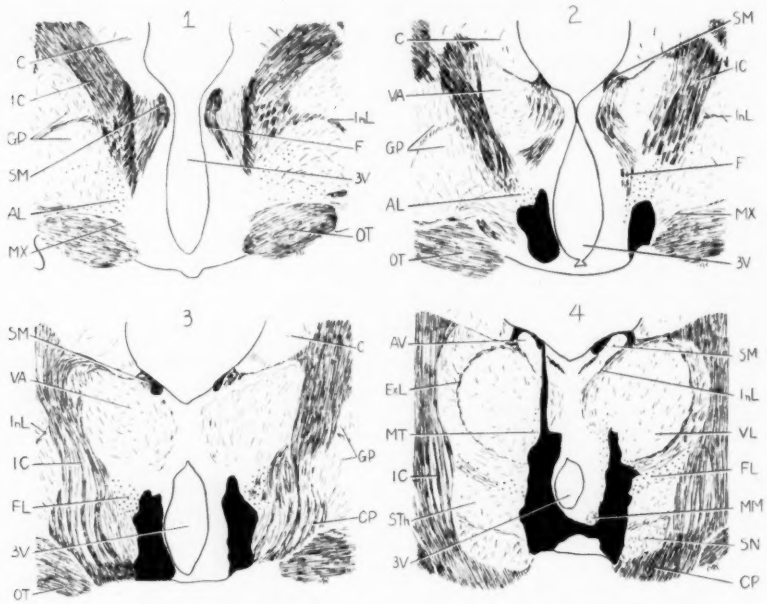


Fig. 4.—Drawings of sections through the brain of monkey 25.

was intact on the right but slightly damaged on the left. Nonobstructive dilatation of the third ventricle, caused by atrophy of hypothalamic structures, was more marked in this brain than in those of the other animals.

There were 11 monkeys with lesions involving the caudal part of the hypothalamus. Ten of these were somnolent for periods ranging from four to eight days and drowsy for somewhat longer periods. One (monkey 38) was not sleepy. Nine were tame and unafraid throughout the period of drowsiness; 2 (monkeys 38 and 40) were only slightly tamed. The drowsiness and emotional stolidity were more prolonged in monkeys 20 and 25 than in the others, but otherwise the behavior of these 2 monkeys and the lesions observed in the brains may be regarded as typical. Slowness, decreased activity and lack of motor

initiative were characteristic of the group. Muscle tonus did not seem to be altered in the 5 monkeys in which it was tested. Anorexia requiring tube feeding for periods ranging from eight to thirty-one days was seen in 8 of the 11 monkeys. When the monkeys ate voluntarily, it was not uncommon for them to go to sleep with the mouth full of food. Four of the monkeys were weak and lay motionless on their sides, but in only 1 was this associated with damage to the internal capsule. Myoclonic jerking was noted in 5 of the monkeys. All except monkey 38 showed a strong grasp reflex and would hang from a rod supported by the arms.

The lesions were similar in the various monkeys of this group. The lateral hypothalamic area was seriously damaged or destroyed bilaterally in all. Except in monkey 38, the lesions in this area extended to the caudal border of the mamillary bodies. The posterior hypothalamic nucleus was seriously damaged or destroyed in all but 3 animals, the least damage having occurred in monkey 38. The mamillothalamic tract was interrupted bilaterally in 6 animals and extensively damaged in all the others except monkey 38. The mamillary nuclei were destroyed in 5 monkeys and damaged in all the others. The majority of the pallidofugal fibers were interrupted bilaterally in 7 animals, and in the others a varying number of these fibers were destroyed. The internal capsule was intact except in 2 of the monkeys.

The lesions in monkey 38, the only one of the 11 animals which did not become somnolent, did not extend quite as far caudally as in the other monkeys of this group; it was the only animal in which the mamillothalamic tracts were intact bilaterally. This animal requires special consideration because it differed so much from the others in its behavior.

MONKEY 38.—This animal had a slightly subnormal temperature for eighteen days. It did not require to be kept in the incubator after the third day and thereafter was housed in a room the temperature of which varied from 74 to 78 F. On the fourth, fifth and tenth days the rectal temperature was normal, but on other days up to the eighteenth was slightly subnormal. The lowest temperature recorded was 98.5 F., which should be compared with the normal of 101 F.

Sleep.—At 8:30 a. m. on the first day after operation the monkey was asleep, but woke when the cage door was opened and was then lively. At noon the monkey was not sleepy. It was awake and alert each morning thereafter, although the man in charge of the animals reported seeing it asleep later in the day.

Emotional Reactivity.—This was slightly reduced. On the first and second days the monkey would retreat to the rear of the cage and when caught would struggle and bite and show considerable emotion, although it was less wild than a normal monkey. It was tamer on the third, fourth and fifth days, could be caught easily and showed little excitement. It remained somewhat subdued as late as the fourteenth day, on which the following note was made: "Not much afraid, but tries to avoid being caught and will bite. Face shows little play of

emotion, but has an alert look. When drawn to the front of the cage, the animal remains calm." On the seventeenth day and thereafter the monkey became increasingly wild and excitable, although it was handled as much as before. On the twenty-first day the monkey tried to jump through the door and put up a good fight when caught. The face remained immobile and masklike except for opening the mouth to bite.

Motility.—This showed no impairment except for slowness of movement. The monkey was active; it would not hang on the rod, and there was no grasp reflex.

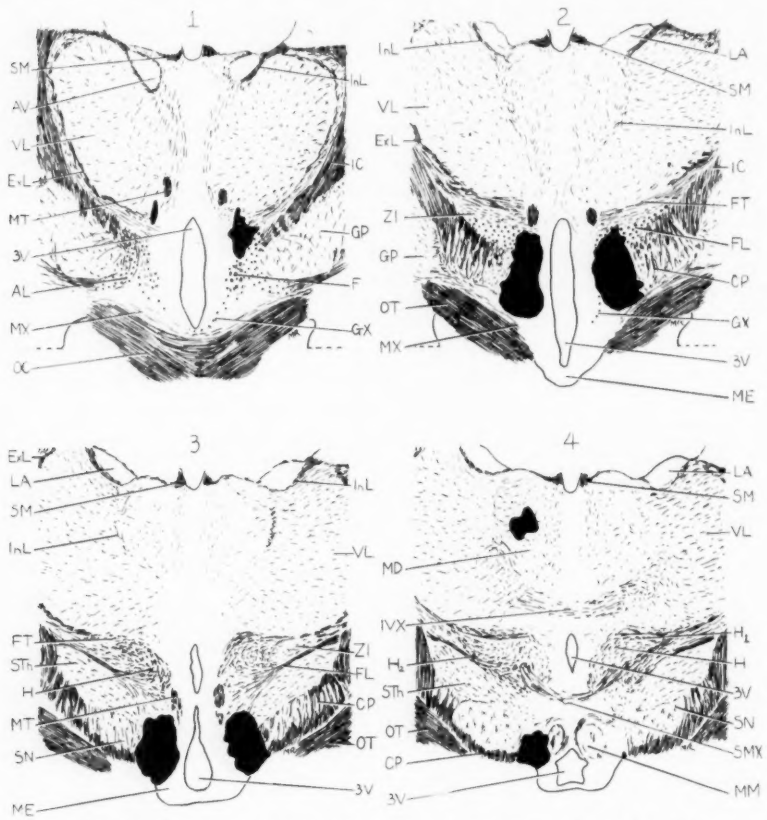


Fig. 5.—Drawings of sections through the brain of monkey 38.

Gastrointestinal Symptoms.—These were lacking. The animal ate well from the first day after operation.

Lesions in the Brain of Monkey 38 (fig. 5).—The internal capsule, basis pedunculi and medial lemniscus were intact. The thalamus was intact except for the two slender tracts left by the insertion of the electrode and one small lesion in the nucleus dorsomedialis. The nucleus filiformis, nucleus supraopticus and nucleus ovoideus were intact; the nucleus hypothalamicus ventromedialis was damaged. The nucleus tuberis lateralis was not visible on either side. The nucleus hypothalamicus posterior was not encroached on by the lesions, but showed an increase in glia cells. The lateral hypothalamic areas, including the nucleus

hypothalamicus lateralis and nucleus ansae lenticularis, were destroyed on the left and badly damaged on the right, from the level of the posterior border of the optic chiasm to the level of the mamillary bodies. On the right side the lesion extended caudally along the lateral side of the mamillary body to its caudal end. On the left the lesion ended near the rostral end of the mamillary body. On the right side the mamillary nuclei were all badly damaged. On the left the nucleus mamillaris medialis contained an excessive number of neuroglia nuclei; the nucleus mamillaris lateralis and nucleus intercalatus could not be recognized. The fornix was interrupted on both sides; the mamillothalamic tract was intact on both sides. The supramamillary commissure and habenulopeduncular tracts were intact. The mamillary peduncle was interrupted on both sides. The substantia nigra and subthalamic nucleus were intact. Many of the large cells were missing in the globus pallidus. The lesions interrupted the ansa lenticularis and a large part of the fasciculus lenticularis, the damage being somewhat more extensive on the left than on the right. More of the pallidofugal fibers were left intact in this animal than in monkeys 20 and 25. Field H of Forel was intact on both sides for a long distance above the red nucleus, and these nuclei were also intact.

Although monkey 38 was seen asleep on the first morning after operation and was reported by the caretaker to have slept at other times, it could not properly have been said to be somnolent. It showed only a moderate decrease in emotional reactivity. The lesions (fig. 5) differed from those in somnolent monkey 25 (fig. 4) chiefly in the greater damage done in the latter to the caudal part of the hypothalamus, including the fields H of Forel, the lateral hypothalamic areas, the posterior hypothalamic nuclei and the mamillary nuclei. The mamillothalamic tracts were interrupted in monkey 25 and bilaterally intact in monkey 38.

Another monkey (no. 39) requires special consideration because it was the only one which was cataleptic. There was nothing peculiar about the lesions in this animal which could be recognized as the cause of the catalepsy. Possibly, the low body temperature may have been a factor.

MONKEY 39.—This animal had a markedly subnormal temperature for thirty-one days after the operation. On the fifteenth day after operation it had a rectal temperature of 94.3 F., although it was in an incubator varying in temperature from 84 to 86 F. It was somnolent for five days and drowsy for eighteen days more. On the twenty-third day the monkey was observed sitting quietly with eyes closed, as if asleep. Occasionally it nodded. The forward movement of the head was followed by a forward movement of the body until the balance was lost. Then, with a quick movement the animal regained its former position; all this was repeated many times. The monkey was entirely unafraid, had an expressionless, masklike face and remained tame and easily handled for the forty days that it was allowed to live. It required tube feeding for thirteen days.

There were marked slowing of movement and loss of motor initiative, but no paresis. The grasp reflex was strong and sufficient to support the weight of the animal when hanging from a rod. Odd postures, into which it was molded, were retained (fig. 6). The catalepsy was unmistakable and persisted for five days;

traces were present as late as the eleventh day. This monkey was the only one that could be said to be cataleptic although slight evidences of a similar state were seen in a few others.

Lesions in the Hypothalamus of Monkey 39.—These were small and destroyed bilaterally the lateral hypothalamic area from the level of the posterior border of the optic chiasm through the mamillary region. The ansa lenticularis and fasciculus lenticularis were largely, but not completely, interrupted on both sides. The mamillary nuclei were badly damaged, and the mamillothalamic tract was interrupted on both sides. There was some damage to the internal capsule on both sides at the level of the anterior end of the thalamus. Large lesions were present in the pars anterior of the ventral nucleus of the thalamus on each side.

Six other animals had good symmetric lesions more rostrally situated in the lateral hypothalamic area. In none of these was the region lateral to the mamillary bodies involved. Only 2 of the 6 monkeys were deeply somnolent, 1 for four days and the other for twelve. Three of the monkeys were awake and alert on the morning after the opera-

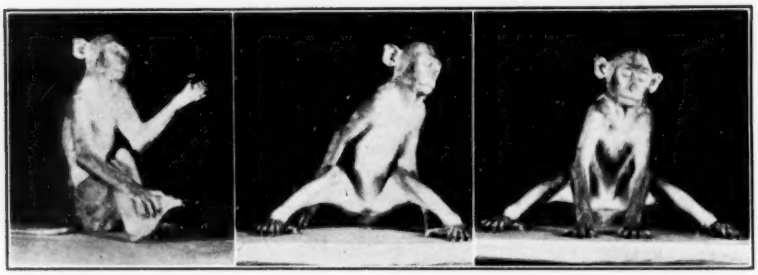


Fig. 6.—Monkey 39 on the third day after operation, illustrating catalepsy.

tion and gradually became drowsy during the course of the first postoperative day and remained so for a few days (one, two and five days, respectively). None of these monkeys were as tame as monkeys 20 and 25, and the tameness did not last as long. After one or two weeks they became increasingly wild.

In none of these 6 monkeys were the mamillothalamic tracts, the mamillary nuclei or the posterior hypothalamic nuclei damaged. In 1, monkey 6, which was somnolent for twelve days, there was extensive damage of the internal capsule. In another, monkey 13, which was somnolent for four days, the internal capsule on the right side was damaged to a slight extent.

Monkey 13.—This animal showed no marked loss in capacity to keep the body temperature up to normal. No paralysis was detected, and there was no rigidity in any of the limbs. The monkey was somnolent for four days and drowsy for five more. It showed the emotional stolidity commonly seen in animals with hypothalamic lesions, but it became progressively wilder after the fourteenth day. Its activity was reduced and slowed. A grasp reflex was present and was strong enough to support the weight of the animal when it hung from a rod. This

animal was similar to monkeys 20 and 25, except that the somnolence and emotional stolidity were not as deep and did not last as long.

Lesions in Monkey 13.—These destroyed the lateral hypothalamic areas to the level of the rostral border of the mamillary bodies (fig. 7). The ansa lenticularis was interrupted on both sides, and there was slight damage to the fasciculus lenticularis bilaterally. The internal capsule was damaged on the left side at the level of the anterior end of the thalamus. The mamillothalamic fasciculus was intact on both sides. The mamillary nuclei and the posterior hypothalamic nuclei were not injured.

In 9 monkeys the lesions were placed too far dorsally, at the junction of the thalamus and the hypothalamus, involving the fields of Forel

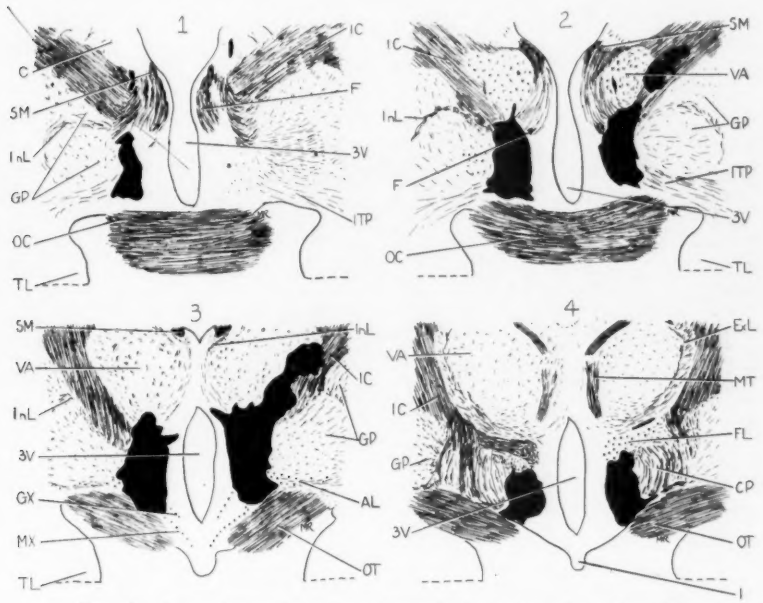


Fig. 7.—Drawings of sections through the brain of monkey 13.

but not damaging the lateral hypothalamic area. Monkey 30 (fig. 8) may be given as an example. It never became somnolent, but remained alert and active and was not much tamer after the operation than before. Somnolence occurred in 5 of the 9 animals, but it lasted for only two or three days. Three of the monkeys behaved like 3 of the 6 with more rostrally located lesions. They had recovered from the anesthesia and were alert and wild on the first morning after operation, then gradually became tame and drowsy. In the case of these animals, it was impossible to avoid the thought that sleep was caused not by the original lesion but by the reaction which occurred around it. Edema and pressure may well have temporarily thrown neighboring structures out of function.

Six of the 9 monkeys were wild on the first morning after operation, and of these, 3 subsequently became drowsy, 2 during the course of the first day and 1 not until the third day. The other 3 remained wild throughout the period of observation. In no case did these animals remain tame for a long time, the longest period being fifteen days. Usually, within a few days after the operation they began to grow wild again.

All the lesions so far described were laterally placed. Two monkeys with medially placed lesions will now be described. Monkey 15 is of

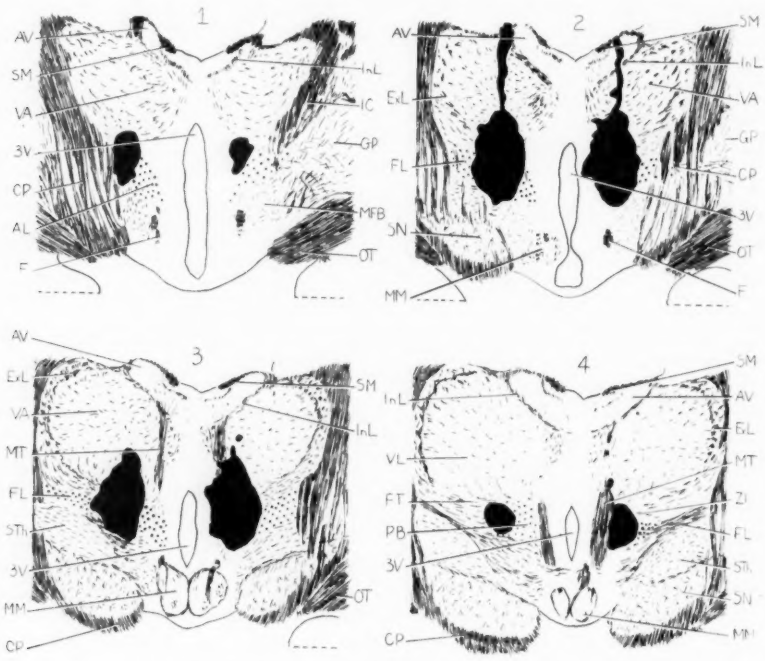


Fig. 8.—Drawings of sections through the brain of monkey 30.

importance because the mamillothalamic tracts, mamillary nuclei and gray matter around the third ventricle, with the periventricular fibers it contains, were destroyed. Monkey 11 had lesions involving the rostromedial part of the hypothalamus. Neither of these monkeys became somnolent, although monkey 15 was at times somewhat drowsy.

Monkey 15.—This animal showed no disturbance in regulation of temperature after the operation. On the morning following the operation it was awake and alert. On the second and seventh days it was drowsy, but never showed anything like the deep somnolence exhibited by monkeys 20 and 25. Emotional reactions were somewhat subdued. Although less afraid than a normal monkey, it avoided one and struggled and bit when caught. There was forced movement to the right; the face and eyes were turned to the right; the animal circled to the right and

was awkward in his movements. There was a grasp reflex in the left hand. In walking the left limbs seemed weaker and more awkward than the right.

Lesions in Monkey 15.—These involved the medial part of the posterior portion of the hypothalamus and subthalamus and the left side of the thalamus (fig. 9). The gray matter surrounding the third ventricle was destroyed from the level of the habenulopeduncular tract, near the cerebral aqueduct, nearly to the rostral end of the thalamus; with it, the periventricular fibers were destroyed. The internal capsule, basis pedunculi and medial lemniscus were intact. The field H of Forel was destroyed on the left side, but was intact on the right. In view of the fact that the internal capsule, basis pedunculi, subthalamic nucleus and substantia nigra were not damaged on either side, I am inclined to attribute the impaired motility of the left legs to the destruction of the H field of Forel on

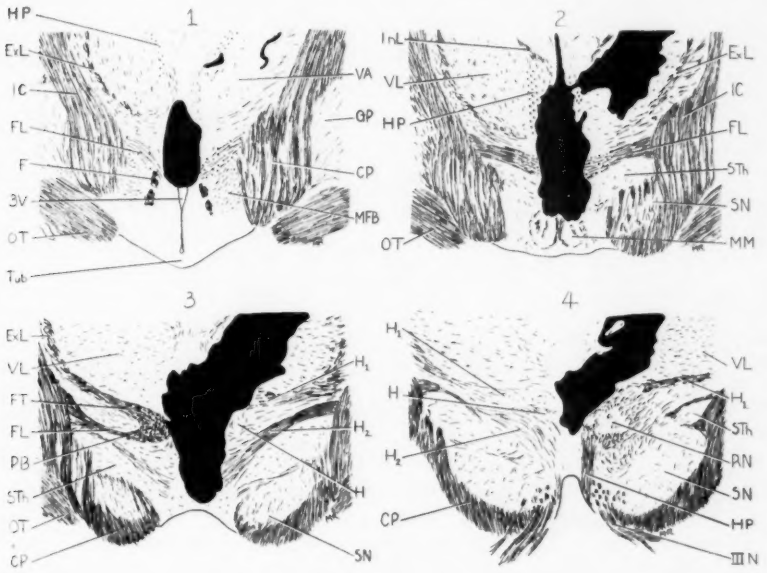


Fig. 9.—Drawings of sections through the brain of monkey 15.

the left side. All the nuclei in the hypothalamus in front of the mamillary bodies were intact. The nucleus hypothalamicus posterior and all the mamillary nuclei were destroyed by the lesion or had lost their cells, which had become replaced by glia to such an extent that the outlines of the nuclei were barely visible in cresyl violet preparations. The mamillothalamic tract was interrupted on both sides. The fornix was not interrupted, but could be traced into the degenerated mamillary body. The lateral hypothalamic area was intact on the right, but was damaged in its medial part on the left.

The slight drowsiness and somewhat decreased emotional excitability in monkey 15 may perhaps be explained by interruption of the connections of the hypothalamus with the thalamus, and thence with the cortex, due to destruction of the mamillothalamic tracts and the periventricular

fibers. It is important, however, to note that although these ascending connections of the hypothalamus were completely interrupted, the drowsiness and decreased excitability did not approach in degree the somnolence and emotional stolidity seen in such preparations as monkeys 20 and 25. Moreover, the delay in the appearance of drowsiness indicates that the structures primarily destroyed by the lesions were not those responsible. The drowsiness and decreased emotional reactivity were no greater than in some of the monkeys of the preceding group, in which the lesions were situated too far dorsally and probably produced their effect by involvement of surrounding structures by swelling and edema.

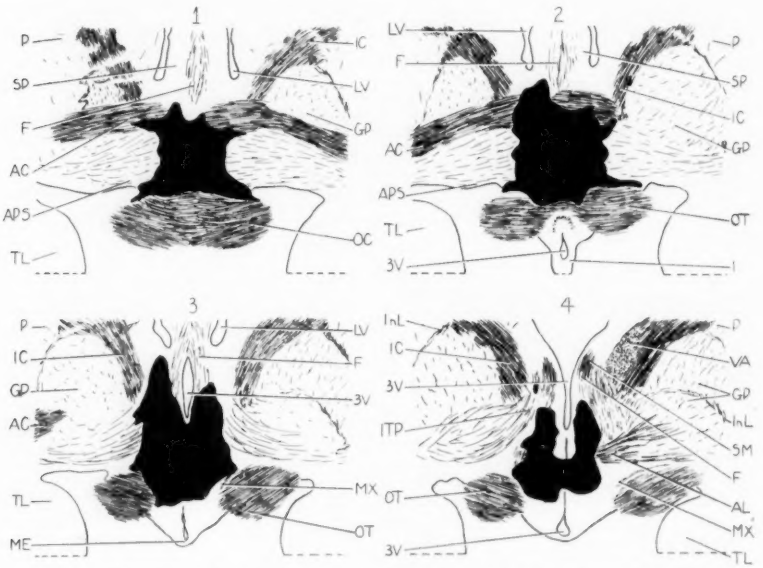


Fig. 10.—Drawings of sections through the brain of monkey 11.

Monkey 11.—This animal had a normal temperature on the morning after the operation. It was alert and active and never appeared to be drowsy. It remained rather wild, but less so than a normal monkey. There was no grasp reflex and no myoclonic movements. It had, after the first postoperative day a good appetite; in fact, it seemed unusually hungry and ate large quantities of food. However, it gained only 140 Gm. in thirty-two days and showed no tendency to adiposity. The lesions in monkey 11 are shown in figure 10. They occupied the anterior part of the hypothalamus and extend above the chiasm into the preoptic region. The supraoptic nuclei were damaged, and the filiform, ovoid, anterior hypothalamic and ventromedial hypothalamic nuclei were destroyed. All the caudal and most of the rostral part of the lateral hypothalamic area was intact. The posterior hypothalamic nucleus, the mamillary nuclei and the mamillothalamic tracts were intact.

COMMENT

In cases of somnolence resulting from hypothalamic lesions in man there is, when once the patient has been wakened, usually no impairment of sensation or motion. In line with this is the fact that in the monkeys in this series the basis pedunculi and medial lemniscus were intact, and often there was no damage to the internal capsule. Such damage as occurred involved the anterior limb or genu. Sleep was not caused by blocking the conduction of impulses to or from the cerebral cortex. For the explanation of the somnolence one must, therefore, take into consideration the normal function of the hypothalamus.

Animals from which all the brain above the hypothalamus has been cut away are very excitable, and this excitability disappears when the hypothalamus is also removed. Bard [4] found that hypothalamic cats respond to slight stimulation by struggling, clawing and snarling and by widespread sympathetic discharge, causing erection of hair, sweating and elevation of blood pressure. At the same time, the respiratory rate becomes rapid. The reaction complex is unmistakably that of rage. It has been found in this laboratory that electrical stimulation of the hypothalamus in waking cats by electrodes, properly placed in the brain and immovably fixed to the skull, causes similar generalized somatic and sympathetic activation.[5] The rise in blood pressure, increases in respiratory rate and dilatation of the pupils caused by hypothalamic stimulation have been studied in more detail in anesthetized animals.[6] With the animal under anesthesia, the visceral reactions always appeared first, but if stimulation of the hypothalamus was continued the excitation

4. Bard, P.: A Diencephalic Mechanism for the Expression of Rage with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490, 1928; The Central Representation of the Sympathetic System as Indicated by Certain Physiologic Observations, Arch. Neurol. & Psychiat. **22**:230 (Aug.) 1929; On Emotional Expression After Decortication with Some Remarks on Certain Theoretical Views: I, Psychol. Rev. **41**:309, 1934; On Emotional Expression After Decortication with Some Remarks on Certain Theoretical Views: II, ibid. **41**:424, 1934. Bard, P., and Rioch, D. McK.: A Study of Four Cats Deprived of Neocortex and Additional Portions of the Forebrain, Bull. Johns Hopkins Hosp. **60**:73, 1937.

5. Kabat, H.; Anson, B. J.; Magoun, H. W., and Ranson, S. W.: Stimulation of the Hypothalamus with Special Reference to Its Effect on Gastrointestinal Motility, Am. J. Physiol. **112**:214, 1935.

6. Ranson, S. W., and Magoun, H. W.: Respiratory and Pupillary Reactions Induced by Electrical Stimulation of the Hypothalamus, Arch. Neurol. & Psychiat. **29**:1179 (June) 1933. Ranson, S. W.; Kabat, H., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of the Hypothalamus, Preoptic Region and Septum, ibid. **33**:467 (March) 1935. Kabat, H.; Magoun, H. W., and Ranson, S. W.: Electrical Stimulation of Points in the Forebrain and Midbrain: The Resultant Alterations in Blood Pressure, ibid. **34**:931 (Nov.) 1935. Kabat, H.: Electrical Stimulation of Points in the Forebrain and Midbrain: The Resultant Alterations in Respirations, J. Comp. Neurol. **64**:187, 1936.

spread to somatic motor centers, and running movements, or even struggling, occurred. The hypothalamus is the center for integration of the sympathetic and somatic reactions involved in emotional expression, and its activation produces a thoroughly excited animal with active visceral and skeletal musculature.

It is probable that the active hypothalamus discharges not only downward through the brain stem, spinal cord and peripheral nervous system into the body but also upward into the thalamus and cerebral cortex. This upward discharge may well be associated with emotion as a conscious experience. This is in line with Cannon's theory.[7] There are known paths between the hypothalamus and the thalamus and cerebral cortex which could account for such interaction.

It has been seen that properly placed lesions in the hypothalamus produce results which are the opposite of those caused by hypothalamic stimulation. Emotional reactions are decreased or abolished, and in place of excitement there is drowsiness or somnolence. It is reasonable to assume that elimination of the excitation caused by hypothalamic activity is responsible for the somnolence and that under normal conditions the hypothalamic drive plays a large part in maintaining the waking state.

Kleitman and Camille[8] emphasized the importance of decreased sensory reception in the production of sleep as follows:

> The state of wakefulness may be produced and maintained by the stream of afferent impulses from surface receptors, proprioceptors, and the visceral receptors, especially the latter. . . . The diminution of this stream of impulses, when it reaches a certain critical value, results in a raising of the threshold of reflex irritability, producing sleep. . . . The great variety of afferent impulses reaching the cerebral cortex is sufficient to keep the animal awake for a long time, not indefinitely. Sooner or later darkness will diminish the number of visual impulses, fatigue will lead to muscular relaxation and a decrease of proprioceptive impulses, and so on, until sleep is precipitated. . . . Most people can fall asleep not only at their habitual bedtime, but almost any time, if a condition is brought about where the number of afferent impulses reaching the cerebral cortex is greatly reduced.

The quotations given, while they fail to account for the sudden passage from the waking to the sleeping state when the critical level of sensory reception has been reached, offer by far the best statement of the conditions which lead to sleep. They are of importance in this discussion because destruction of the hypothalamus leads to exactly these conditions by abolishing the sympathetic and somatic excitation

7. Cannon, W. B.: The James-Lange Theory of Emotions: A Critical Examination and an Alternative Theory, Am. J. Psychol. **39**:106, 1927.

8. Kleitman, N., and Camille, N.: Studies on the Physiology of Sleep: VI. The Behavior of Decorticate Dogs, Am. J. Physiol. **100**:474, 1932.

resulting from hypothalamic activity. The bodily quiet which follows destruction of the hypothalamus is probably partly responsible for the somnolence, but in this connection the drive normally exerted by the hypothalamus on the rest of the brain should not be overlooked.

The occurrence of somnolence as a result of lesions destroying vegetative centers in the hypothalamus has led to the formulation of theories which would explain sleep as due to preponderance of parasympathetic over sympathetic activity. Some support is given this point of view by the small pupils, slow pulse and decreased blood pressure usually seen in sleep, but these may as well be due to decreased sympathetic as increased parasympathetic activity. Hess [9] expressed the belief that parasympathetic impulses cause sleep by active inhibition. There is no reason to assume, however, that the part of the brain that he stimulated in his experiments with sleep has parasympathetic functions. Hess [10] said:

Eigentlichen Schlaf als Effekt einer zentralen Reizung erhielten wir niemals aus dem Hypothalamus, mit bemerkenswerter Konstanz dagegen aus dem Grenzgebiet von Subthalamus und Thalamus, und zwar in jenem Bereich, welcher sich in dieser Höhenlage vom Vicq d'Azyrschen Bündel nach vorn und etwas mehr nach hinten erstreckt.[11]

Moreover, Harrison [12] has not been able to confirm Hess's observation that sleep can be produced by stimulation.

The idea that the parasympathetic fibers play any essential role in the production of sleep cannot be accepted, because if this were true sleep would be prevented by administration of full doses of atropine, which is not the case. Ephedrine, a sympathetic stimulant, is an almost specific remedy in cataplexy, but whether its value in preventing drowsiness is due to its action on the sympathetic system or to stimulation of the central nervous system is not definitely known.

Since the somnolence caused by hypothalamic lesions cannot be attributed to parasympathetic activity, left unbalanced by the destruction of sympathetic centers, there remains as the only reasonable explanation the quiet and relaxation which result when the emotional drive of the hypothalamus is eliminated. It is probable that this drive is exerted upward on the thalamus and cerebral cortex, as well as downward

9. Hess, W. R.: The Autonomic Nervous System, Lancet **2**:1199 and 1259, 1932.

10. Hess, W. R.: Hypothalamus und die Zentren des autonomen Nervensystems: Physiologie, Arch. f. Psychiat. **104**:548, 1936.

11. We have never produced true sleep as an effect of stimulation of the hypothalamus, but have obtained it with remarkable constancy from the border of the subthalamus and thalamus and, indeed, in the region which extends at this level from the bundle of Vicq d'Azyr forward and somewhat posteriorly.

12. Harrison, F.: An Attempt to Produce Sleep by Diencephalic Stimulation, to be published.

through the brain stem, spinal cord and peripheral nervous system. It now becomes necessary to inquire how far the somnolence is due to elimination of the excitatory action of the hypothalamus on the cerebrum.

It will be remembered that of the 11 monkeys with well placed lesions in the caudal part of the hypothalamus only 1 failed to show somnolence and that 1 (monkey 38) was the only animal in which the mamillary bodies and mamillothalamic tracts were intact. These tracts constitute the largest and best defined path for upward discharge from the hypothalamus. The origin of this tract from the medial mamillary nucleus in the caudal part of the hypothalamus might be associated with the fact that lesions in this part of the hypothalamus most regularly cause sleep, and the conclusion might be drawn that removal of the upward drive was the most important factor in producing somnolence. Against this conclusion, however, stand a number of observations. Monkey 15, in which the mamillary nuclei were degenerated, the mamillothalamic tracts interrupted and the periventricular fibers connecting the thalamus and the hypothalamus destroyed, together with the periventricular gray matter of the third ventricle, showed only slight drowsiness, not at all comparable with the somnolence seen in the 10 monkeys with lesions involving the lateral hypothalamic areas to the level of the caudal border of the mamillary bodies. Furthermore, monkeys 6 and 13, in which the mamillary nuclei and the mamillothalamic tracts were not damaged, were somnolent for twelve and four days, respectively. While the mamillothalamic system may play a part in maintaining the waking state, and its desruction may be a factor in somnolence of hypothalamic origin, it is certainly not the most important system in this connection.

All the evidence from this series of experiments points to the lateral hypothalamic area as the region bilateral destruction of which leads to somnolence. It is this same area the stimulation of which produces most readily combined sympathetic and somatic excitation. Small lesions bilaterally placed in the caudal part of this area cause marked disturbance in the capacity to regulate body temperature. The results of stimulation experiments which my colleagues and I have carried out and the study of animals with hypothalamic lesions have led us to conclude that the descending pathways from the sympathetic nuclei of the hypothalamus run caudad in the lateral hypothalamic area. At the level of the mamillary bodies a part of the descending path turns mediad and enters the central gray matter, but the larger part is continued directly downward, lateral and dorsolateral to the mamillary body, into the mesencephalic tegmentum. We believe that it is because of the accumulation of these descending fibers in the lateral part of the hypothalamus that it is so responsive to stimulation and that lesions placed here are so effective in interfering with regulation of temperature and in the production of somnolence.

Because the lesions most effective in the production of somnolence are located in the caudal part of the lateral areas and destroy the descending paths from the hypothalamus, we believe that the somnolence is due in large part to elimination of the downward hypothalamic drive.

In our monkeys the electrodes had passed through the thalamus to reach the hypothalamus, and the line of puncture was marked by a scar. Sometimes there was secondary vascular involvement of the anterior part of the thalamus (fig. 3) or gliosis of the dorsomedial nucleus. Experiments performed by Spiegel and Inaba [13] led them to conclude that somnolence can be caused by thalamic lesions. Although their observations were not in accordance with clinical experience, which indicates that thalamic lesions cause sleep only when there is secondary involvement of the hypothalamus, the question may arise how far the somnolence in our monkeys may have been due to damage to the thalamus. In answer, it can be said that in some of the monkeys the thalamic damage was slight (fig. 4). Moreover, 7 monkeys in which large lesions were intentionally placed in the thalamus failed to show any signs of somnolence. A photograph of the lesions in the brain of 1 of these animals has been published elsewhere.[14]

Demole [15] and Cloetta and his co-workers [16] concluded that the diffusion of calcium ions from the blood to the brain, especially in the region of the infundibulum, is responsible for sleep. However, Cooperman [17] found that the calcium content of the blood is lowered by relaxation without sleep, and he explained the fall in blood calcium during sleep as secondary to the relaxation. In cats made cataleptic by lesions similar to those causing somnolence in monkeys there was no significant change from normal in the amount of calcium in the blood.

Catalepsy.—This was seen in only 1 of the animals (monkey 39). It lacked the initiative necessary to change its position and would retain odd postures for long periods. Some of these poses, such as that shown at the left of figure 6, obviously required sustained muscular contraction. While the other somnolent monkeys remained immobile in normal postures of rest, this was the only animal that retained abnormal and apparently uncomfortable attitudes. Unfortunately, no specific reference was made in the notes concerning the state of muscle tonus in this

13. Spiegel, E. A., and Inaba, C.: Zur zentralen Lokalisation von Störungen des Wachzustandes, Ztschr. f. d. ges. exper. Med. **55**:164, 1927.

14. Ranson, S. W.: Some Functions of the Hypothalamus, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 92.

15. Demole, V.: Pharmakologisch-anatomische Untersuchungen zur Problem des Schlafes, Arch. f. exper. Path. u. Pharmakol. **120**:229, 1927.

16. Cloetta, M.; Fischer, H., and van der Loeff, M. R.: Die Biochemie von Schlaf und Erregung mit besonderer Berücksichtigung der Bedeutung der Kationen, Arch. f. exper. Path. u. Pharmakol. **174**:589, 1934.

17. Cooperman, N. R.: Calcium and Protein Changes in Serum During Sleep and Rest Without Sleep, Am. J. Physiol. **116**:531, 1936.

animal. The lesions did not differ significantly from those in other monkeys. Perhaps the markedly subnormal temperature of this animal may have been a factor. The catalepsy was most marked during the first few days, but was still evident on the eleventh day.

Cats with lesions involving the ventral part of the brain stem from the rostral border of the mamillary bodies to the exit of the third nerve regularly showed catalepsy which persisted for many days or weeks.[3] The lesions in these cats had considerable in common with those in our monkeys, and it has been difficult to understand why more of the monkeys were not cataleptic. In the cats there was an obvious increase in muscle tonus, which was probably an important factor.

Gastrointestinal Symptoms.—Most of the somnolent monkeys refused food and had to be fed by tube for from eight to thirty-one days. Anorexia was also a prominent feature of the syndrome presented by cataleptic cats [3] and is frequently seen in cats with large lesions in the anterior part of the hypothalamus. Vomiting and diarrhea were sometimes seen in the monkeys which were being fed by tube.

The disturbances in regulation of temperature in these monkeys has been described elsewhere.[18] Damage to the pallidofugal fibers and the associated changes in the globus pallidus will be discussed with the motor symptoms in another paper.[19]

There are current three chief theories of sleep, but these are not mutually exclusive. According to Pavlov,[20] sleep is brought about by the spread of inhibition through the cerebral cortex and lower centers, this general inhibition being the result of a conditioned reflex. This conception has the advantage of accounting for the sudden transition from the waking to the sleeping state. In order for the inhibition to be effective, however, Pavlov's dogs had to be at rest in a quiet room. Thus, the conditions for sleep as set forth by Kleitman were fulfilled.

Kleitman's theory emphasizes the importance of quiet and relaxation as conditions necessary for sleep.[8] The resulting decrease in the flow of sensory impulses to the brain results in sleep; since, however, this does not account for the sudden onset of sleep, a conditioned reflex is brought into the picture. The periodic cessation of activity due to nightfall sets up a conditioned reflex which switches off both afferent and efferent connections with the higher centers.[21]

---

18. Ranson, S. W.; Fisher, C., and Ingram, W. R.: Hypothalamic Regulation of Temperature in the Monkey, Arch. Neurol. & Psychiat. **38**:445 (Sept.) 1937.

19. Ranson, S. W., and Ranson, M.: Bilateral Interruption of Pallidofugal Fibers in the Monkey, to be published.

20. Pavlov, I. P.: Lectures on Conditioned Reflexes, translated and edited by G. V. Anrep, London, Oxford University Press, 1928.

21. Kleitman, N.: Studies on the Physiology of Sleep: I. The Effects of Prolonged Sleeplessness on Man, Am. J. Physiol. **66**:67, 1923.

The theory of a so-called sleep center is based on misinterpretation of facts.[22] If the term "waking center" is substituted and the center is placed in the hypothalamus, there is no conflict between this concept and that of Kleitman. We have shown that the hypothalamus is the center for the integration of emotional expression and that when it is active there is excitement. It is therefore a center for waking, and when it is thrown out of function the withdrawal of this source of excitation permits quiet and relaxation, which favor the onset of sleep. The hypothalamus was thrown out of function by Demole [15] by injection of calcium chloride. The lesions in our monkeys acted in the same manner. Clinical evidence fully supports the theory that destruction of the hypothalamus causes somnolence. What is new in this presentation is an explanation of why damage to the hypothalamus causes somnolence and evidence as to what part of the hypothalamus must be involved.

A satisfactory explanation for sleep as such has never been presented. It is known from Kleitman's work what are the conditions necessary for sleep, and the present investigation has offered an explanation for the somnolence following damage to the hypothalamus. What normally causes the sudden change from the waking to the sleeping state and what happens in the different parts of the brain during sleep remain unknown.

---

22. von Economo, C.: Sleep as a Problem of Localization, J. Nerv. & Ment. Dis. **71**:249, 1930.

GENESIS OF MICROGLIA IN THE HUMAN BRAIN

JOHN KERSHMAN, M.D., M.Sc.
MONTREAL, CANADA

The existence of microglia as a cell group in the central nervous system was first described by del Río Hortega in 1919 and has been universally accepted. However, the origin of these cells and their relation to neuroglia [1] has remained controversial.

Certain authors have maintained that microglia and neuroglia have a common origin from the neuroepithelium of the primitive medullary canal. On the other hand, Hortega and many others have expressed the belief that microglia cells are derived from mesenchymal cells and have no direct genetic relationship to astrocytes and oligodendroglia cells. This difference is fundamental and of great significance in understanding the biologic functions of these cells.

With few exceptions, all previous embryologic studies on microglia have been made on laboratory animals. In the present work, the origin and evolution of these cells were traced in a series of human embryos. It was possible to demonstrate that microglia cells are derived from mesenchymal elements and are genetically related to histiocytes. Their embryologic development is different from that of neuroglia cells, which are neuroectodermal in origin.

Nests or fountains of microglia cells were observed in certain constant locations during the development of the brain. These nests, besides being the main foci from which microglia cells are dispersed into cerebral tissue, are habitually related to areas in which tracts are being formed. The migrating microglia cells were observed to follow the direction of growth taken by these tracts. The possible significance of this will be discussed.

REVIEW OF LITERATURE

The first study of the cytogenesis of microglia in human embryos was published in 1932, shortly after the present work was undertaken. Up to that time all observations had been derived from common labora-

---

From the Montreal Neurological Institute.

The words "pathologic," "embryologic" and "morphologic" are used in order to conform to the terminology which is compulsory for publication in the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. The author would prefer to use the words "pathological," embryological" and "morphological."

1. The term neuroglia as used in this paper refers collectively to astrocytes and oligodendroglia cells, as distinct from microglia. This is in conformity with the classification proposed by Penfield (1928) and now generally in use.

tory mammals (rat, mouse and cat). The literature has been completely reviewed by Hortega (1932). Only a brief summary will be given here.

Hortega and his associates (1919 and later) concluded that microglia cells first appear in the cat, rat, rabbit and mouse just before birth or in the newborn animal. They are derived from cells in the meninges and invade the brain mainly from definite areas, known as fountains. The fountain in each case occurs in a zone in which the brain is in immediate contact with mesodermal tissue (the meninges or the mesodermal reflection of the choroid plexuses). In the cerebrum these fountains are around the attachments of the choroid plexuses of the lateral and third ventricles and in the region of the pial lining of the cerebral peduncles. In the cerebellum the main focus is in the pia lining the white surfaces and, especially, in the bulbocerebellar fold constituting the inferior tela choroidea. In the bulbopontile region and the spinal cord microglia also arises from the pia and its folds.

Besides these main foci, microglia cells are also formed in small quantities from the pial elements covering the cerebral and cerebellar folds, particularly from the pial adventitia of large and medium-sized blood vessels. The migrating cells which invade the brain from these sources are ameboid. Each has a lymphocytoid nucleus and a granular, vacuolated cell body and is similar to the compound granular corpuscle seen in the brain during pathologic processes. As they penetrate the central nervous system, these cells move by means of pseudopodia and, when nearing their resting site, become elongated and branched. On reaching their stable location they finally assume the morphologic character of normal resting microglia cells, with typical expansions and fine spines.

Hortega admitted that staining methods are inadequate to determine the exact cell from which microglia elements originate. He expressed the belief, however, that they are formed by the migration into the brain of embryonic mesenchymal corpuscles. He concluded that they are polyblastic cells, related histogenetically to the clasmatocytes of Ranvier, the leukocytoid adventitial cells of Marchand, the polyblasts or resting wandering cells of Maximow and the rhagiocrin cells of Renaut. These cells are all macrophagic elements capable of ameboid movement under similar circumstances.

Penfield (1928) confirmed this derivation of microglia from pial cells and the existence of microglial fountains. He pointed out that the fountains occur in the only areas of the brain where pia comes into close contact with white matter in which myelinization is going on and that this process may have a chemotactic influence on pial elements.

That mesenchymal cells may participate in glia formation was first suggested by Virchow (1846), and the history of this concept was elaborated by Hortega (1932).

In contrast to these opinions, however, a number of authors have insisted that all glia elements have a common genesis and that microglia cells are derived from elements originating in the neural ectoderm, in the same way as astrocytes and oligodendroglia cells.

Pruijs (1927) studied the brains of a series of rabbit embryos and described *stäbformigen,* or "rod-shaped," cells which appear toward the end of embryonic life. These rod-shaped cells are derived from the cells of the ependymal zone; from them, by transitional stages, Pruijs traced the formation of microglia and oligodendroglia cells. According to Pruijs, these two elements are closely related by intermediary forms, and both are neuroectodermal derivatives.

This point of view was supported by Rydberg (1932). He described ameboid cells originating from the ependyma and ectodermal matrix of the cerebral wall in the brains of rabbit fetuses and 1 day old kittens. Rydberg stated that transitional stages can be observed between the ameboid cells and the various kinds of embryonic glia cells and concluded that all the glia elements have a common origin from ependymal zone cells. He denied that mesenchymal elements participate in glia formation.

It is significant that the authors who subscribe to a common origin for all the glia cells are unable to make a clear morphologic differentiation between microglia and oligodendroglia, not only during embryonic development but often in the mature state. As might be expected, it is these authors who support the belief that microglia and oligodendroglia behave similarly during pathologic processes.

Using Bolsi's modification of Hortega's stain, Gozzano (1930 and 1931) made an extensive study of brains of newborn rabbits and confirmed the descriptions by Hortega and Penfield of the genesis of microglia. His charts showing the areas where mesenchymal cells invade the brain corroborate in general the location of Hortega's fountains.

Santha (1932) prepared similar charts. In addition, he was the first to demonstrate that microglia cells can be recognized in the brains of cat, dog and rat embryos much earlier than a few days before birth. Before the midpregnancy period no fat-containing granular corpuscles are observed, but mature microglia cells are present in the nerve parenchyma, usually intimately associated with blood vessels. Santha expressed the belief that their occurrence is directly proportional to the general development of the area concerned.

Belezky (1932) observed in chick embryos that mesoblastic cells begin to invade the brain on the fourth day of incubation. He concluded that these migrating cells develop into both microglia and oligodendroglia cells. Belezky was unable to distinguish sharply between these two types of cells and called them collectively mesoglia. He stained simultaneously these and similar cells in muscle and connective tissue and identified them all as histiocytes.

In 1933 Santha and Juba demonstrated that in rat embryos the earliest appearance of microglia is related to the first evidence of vascularization within the brain. The earliest microglia appears in the rhombencephalon and diencephalon of 15 mg. rat embryos, and these areas are the first to be vascularized. Extracerebral microglia-like cells were also seen, and the authors expressed the belief that microglia has an adventitial origin and probably is also derived from the monocytes of the circulating blood.

Bolsi (1936), in an extensive study, confirmed these observations in rats and other animals.

The first study of the genesis of microglia in man was reported by Rydberg (1932). He examined the brains of a series of newborn infants, most of whom had died as the result of injuries at birth. After describing all the glia forms present, he concluded that transitional forms exist between small spongioblasts, "free" or "naked" nuclei, microglia cells and oligodendroglia cells. He also described the occurrence of "amoeboid glia" cells in the neighborhood of the ependymal matrix and concluded that these elements originate from ependymal cells and may develop into any of the glia forms. According to Rydberg, therefore, microglia cells are of neuroectodermal origin and are closely related genetically to other glia cells.

Santha (1932) succeeded in staining the microglia in 2 human fetuses (30 and 38 cm. in crown-rump length). Almost mature microglia cells were present in the basal ganglia, the cortex and the medulla. Globose and tuberous forms were not seen, although in the tracts and subcortical areas plump branched cells were observed.

Finally, Juba (1933) demonstrated the presence of microglia in a series of human embryos ranging in crown-rump length from 23 to 280 mm. The various cell forms, varying from ameboid elements to mature branched forms, were seen. According to Juba, microglia originates by the invasion and penetration of certain mesodermal cells closely related to embryonic vascular elements. In the connective tissue of the head, microglia-like cells can be stained by the silver carbonate method, and Juba expressed the opinion that microglia cells are genetically related to polyblasts, monocytes and histiocytes. No developmental relationship was seen between microglia and neuroglia cells.

MATERIAL AND METHODS

This study was carried on concurrently with an investigation in which it was attempted to determine whether medulloblasts, or Schaper's indifferent cells, occur during the normal development of the central nervous system. The material used was essentially the same in the two studies and has been described in detail elsewhere (Kershman, 1938).

A series of human embryos was collected specifically for this work; after the possibility of pathologic changes was excluded and the embryos were discarded in which death had occurred more than a few hours before fixation, a series of 22 specimens, ranging in crown-rump length from 25 to 255 mm., was obtained. In addition, a number of infants' brains were examined.

Hortega's method (1919) for staining microglia was used; however, because in many cases the primary fixative was formaldehyde rather than a solution of formaldehyde and ammonium bromide, a number of modifications of this method were employed. Practically all the variations published were tried. Excellent stains for microglia were obtained from material fixed in formaldehyde and treated by Penfield's modification for the combined staining of oligodendroglia and microglia. The sections were placed in the silver solution for one or two minutes only; this gave almost exclusive staining of microglia, especially in young embryos in which the neuroglia was poorly developed. The use of equimolecular solutions made no appreciable difference. Occasionally, exquisitely selective stains were obtained with Hortega's original solution of lithium and silver carbonate (Hortega, 1918) rather than the standard solution of sodium and silver carbonate.

The use of a neutral solution of formaldehyde for both fixation and reduction was advantageous. This was obtained by adding powdered chalk to the stock solution.

Material was stained from two hours to two years after fixation; results were often better after prolonged fixation in formaldehyde. The sections were washed for several hours in weak ammonia water before staining, or the bromuration method was used. In general, microglia stained more selectively if the fixative had not been injected into the brain but small blocks had been cut and fixed separately.

One specimen was fixed in Bouin's solution for four or five days and then stored in 70 per cent alcohol for several weeks. Blocks were then cut and transferred to formaldehyde-ammonium bromide solution and solution of formaldehyde U. S. P. (1:10). After sections were cut they were washed for two minutes in 70 per cent alcohol, followed by rapid passage through a weak solution of ammonia (1:50) or a 5 per cent solution of sodium carbonate before proceeding with the direct Hortega method or the Penfield modification. Excellent microglia stains were obtained in this way.

The Herxheimer fat stain was combined with the silver carbonate method, as outlined by Penfield and Cone (1928). In addition, the usual dye stains were used.

OBSERVATIONS

Microglia cells were found in every specimen of the series (from the 8 week embryo).

Spinal Cord.—At the 8 week stage (25 mm., crown-rump length) the nervous system is already vascularized and surrounded by the primitive meninges. The morphologic pattern and distribution of microglia in the spinal cord at this age is shown in figure 1. The character of the spongioblastic framework is indicated in the background.

There were few microglia cells in the ependymal and mantle zones. Those present were elaborately branched elements the rambling expansions of which insinuated themselves between the spongioblasts. The nuclei of the microglia cells were densely granular and irregular. Morphologically, these cells were in

marked contrast to the closely packed, simple polarized spongioblasts, with large oval nuclei, which crowded the ependymal and mantle zones at this age.

In the comparatively acellular marginal zone, the relative distribution of cells was reversed. Here, almost all the cells were diverse forms of microglia. Beneath the meninges in the posterolateral angle (where accumulating nerve fibers form the anlage of the posterior columns) a group of ameboid microglia cells

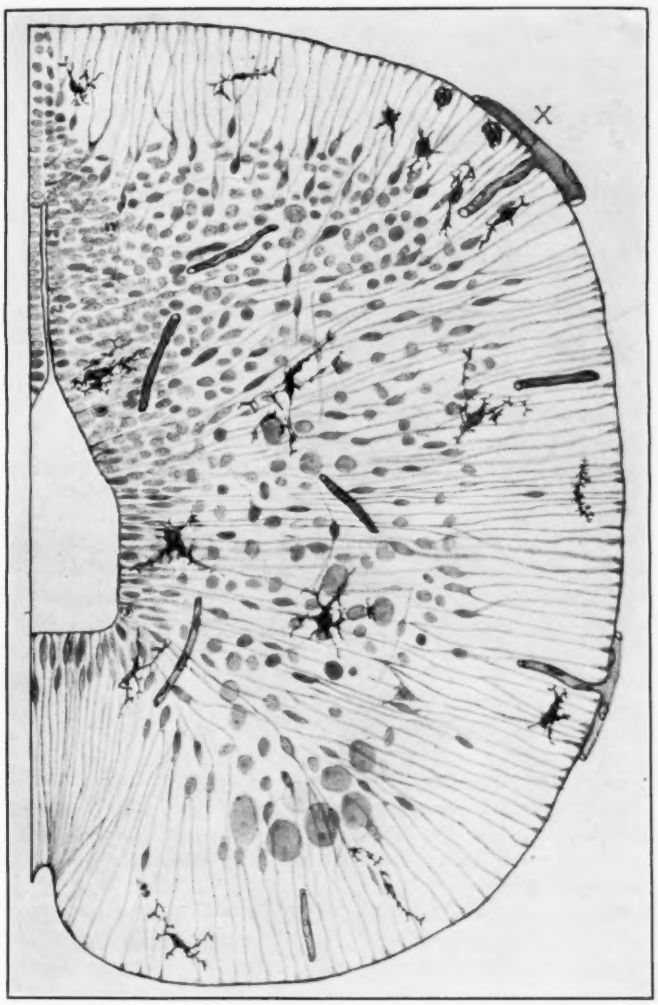


Fig. 1.—Composite drawing showing distribution of microglia in the spinal cord of an 8 week human embryo. The spongioblastic framework is faintly indicated in the background. *X* indicates the posterolateral region where a small nest of ameboid and pseudopodic microglia cells occurs around the blood vessel. Silver carbonate stain.

was seen around a blood vessel (fig. 1 *X*). Similar ameboid forms were seen just under the meninges elsewhere. Each ameboid cell had a densely staining, spherical nucleus, and the cell body was a wide mantle of irregular, spongy cytoplasm containing granules and vacuoles of varying sizes (figs. 1 and 2 *A* and *B*). In some microglia cells of the marginal zone part of the cytoplasm was drawn out into a broad, blunt pseudopodic expansion, and in others several thinner expansions were present, with varying degrees of branching (figs. 1 and 2 *C* and *D*). Many transitional forms were seen in which the cells were more irregular and the cytoplasm was drawn out into fine prolongations, occasionally bearing secondary spines. These elements were morphologically similar to the microglia cells seen in the mantle and ependymal zones (figs. 1 and 2 *E* and *F*).

That microglia cells can assume such varied morphologic forms has been amply confirmed by the tissue culture experiments of Marinesco and Minea (1930), Wells and Carmichael (1930), Costero (1931) and Dunning and Furth (1935), in which the transformations were directly observed. Pathologists are generally agreed that similar changes take place in vivo (Penfield, 1928; Hortega,

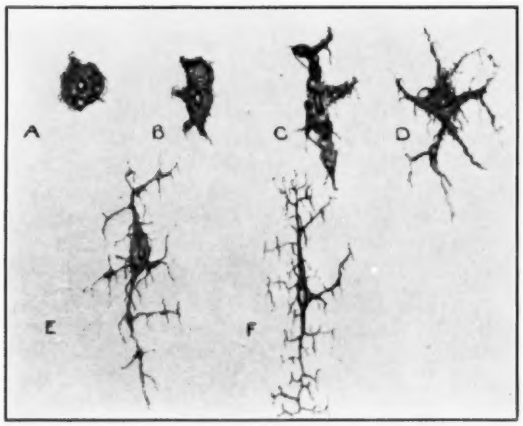


Fig. 2.—Drawing showing stages in the differentiation of microglia cells. *A* is an ameboid form; *B* and *C* are pseudopodic forms; *D* is an early branched form; *E*, a more branched form, and *F*, a mature microglia cell. Silver carbonate stain.

1932). The ameboid and pseudopodic cells are recognized as the mobile migratory forms of microglia, while the branched cells are more stable forms. In the embryos in the present series, selective staining confirmed the unity of these protean microglia elements.

When the spongioblasts and other cells derived from the ependymal zone were completely stained with silver carbonate, no cell forms were observed suggesting intermediary or transitional stages between them and any variants of microglia cells.

With the growth of the nervous system, microglia cells became more numerous and widespread. In the spinal cord at the 11 week stage, they were observed to be more evenly distributed in the different zones than at the 8 week stage. At the same time, with growth there was a relative increase in the stable branched forms and a diminution in the mobile ameboid and pseudopodic cells. In tract regions elongated pseudopodic microglia cells were seen lying parallel to the fibers, though often branches crossed them. After about the 20 week stage

ameboid forms were rare in the spinal cord, and only well branched cells were seen. After this age, also, the microglia cells became more numerous in the gray matter (mantle zone) than in the white (marginal zone), thus reversing the initial relationship. This is the normal distribution in the adult.

There was no noticeable increase in microglia during myelination of the spinal cord. It was observed, however, that the process of myelination was always preceded by accumulation of oligodendroblasts (Kershman, 1938). These oligodendroblasts were formed from apolar spongioblasts derived by migration from the ependymal zone and from the mitotic division of polar spongioblasts. There was no evidence of transitional forms between these cells and microglia elements. On the other hand, the changes in number and distribution of ameboid and branched microglia cells during growth provided fair evidence for concluding that the stable forms are derived from the ameboid migratory cells. This will be discussed further.

Brain Stem and Cerebellum.—In the brain stem and cerebellum microglia cells gradually increased in number in the same manner as in the spinal cord, except that the process was much slower. Microglia cells were at first (8 week embryo) most numerous in peripheral regions (marginal and submeningeal zones), and their predominant form was the ameboid and the pseudopodic mobile cell. Centrally or deep in the brain substance, few microglia cells were seen, and these were the more stable branched forms. With growth, the stable microglia cells accumulated, with gradual disappearance of the ameboid elements at the periphery.

A typical microglial fountain was seen in the rhombic furrow of the 8 week embryo. The cerebellum is formed as an elaboration of the alar plate of the rhombencephalon cephalad to the pontile flexure. Growth of this plate causes it to bulge outward, so that on the lower part of its outer surface a shallow furrow is formed, which delimits it from the pons below. This is known as the rhombic furrow (*aüssere Lippenfürche,* or outer rhombic lip of Jacob, 1928). In the V-shaped marginal zone beneath this furrow there was an accumulation of ameboid microglia cells (fig. 3). When counterstained with scarlet red, most of these cells were seen to contain fat droplets. Occasionally one was in mitotic division.

Radiating inward from this zone there were more elongated pseudopodic microglia cells containing a few lipoid granules, while deeper in the cerebellum and hindbrain only an occasional microglia cell, always complexly branched, was seen.

Between the cerebellum and the pons at this age the cerebellar peduncles are being formed (His, 1904; Streeter, 1912), and their site is in the same region as the microglial nest. A smaller, but similar nest was seen a short distance anteriorly.

With the method of Penfield for combined staining of oligodendroglia and microglia, it was possible on many occasions to demonstrate selectively ameboid and pseudopodic cells in the meningeal investment of the hindbrain and cerebellum at the same time as intracerebral microglia cells. Morphologically, the intracerebral and extracerebral cells were remarkably similar. Staining with scarlet red showed that fat droplets were often present in the ameboid cells of the surrounding meninges, as well as in the ameboid microglia cells of the underlying marginal zone of the brain. Figure 4 shows several fat-containing cells around a capillary in the marginal zone of the medulla and similar cells in the meninges at the 12 week stage.

In general, the parts of the brain which mature earlier acquired stable, branched forms of microglia sooner. Thus, the spinal cord and medulla con-

tained only stable, branched microglia cells comparatively early, no ameboid forms being seen after about 20 weeks.

In the cerebellum, however, the cortex was relatively slow in developing, and large numbers of ameboid microglia cells were still present in the marginal zone in the 27 week embryo (fig. 7 *3*). At the same time, in the meninges overlying the cerebellum many ameboid microglia-like cells were demonstrated with the silver carbonate method. Transitional forms between these cells and the

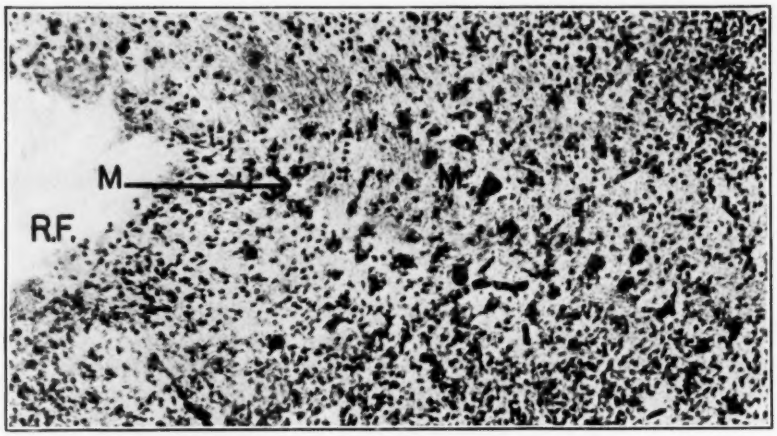


Fig. 3.—Photomicrograph from the region of the rhombic furrow (*R. F.*) between the cerebellum and the pons in an 8 week embryo, showing a nest of ameboid microglia cells (*M*) just under the furrow. Silver carbonate stain.

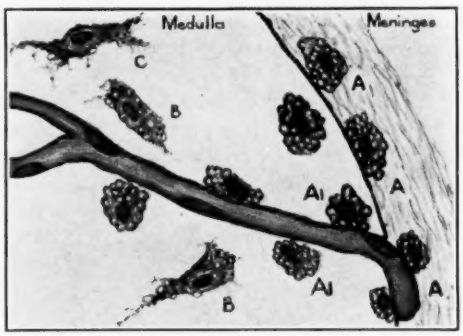


Fig. 4.—Drawing of a portion of the medulla of a 12 week human embryo. Fat-containing ameboid cells (*A*) are present in the meninges and accompany a blood vessel into the medulla, where they form ameboid microglia cells (*A 1*). A short distance from the blood vessel are pseudopodic forms (*B* and *C*). Silver carbonate stain.

ameboid and pseudopodic microglia cells within the cerebellum were obvious (fig. 7 *3*).

Forebrain.—At 8 weeks the hemispheral wall was too thin for study by the microglia technic. At this age the distribution of microglia cells in the dien-

cephalon was the same as that in the spinal cord. In the marginal zone ameboid microglia cells were often seen attached to the walls of a capillary, and occasionally one of these cells was undergoing mitotic division (fig. 5).

At 11 weeks the hemispheral wall contained pseudopodic and branched microglia cells. Most of them were in the marginal zone, but some were seen in the

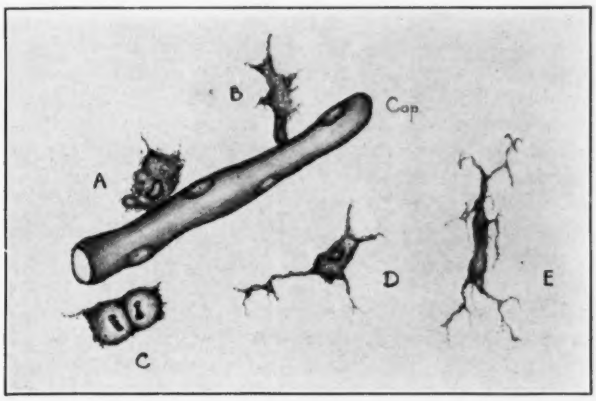


Fig. 5.—Drawing showing microglia cells in the marginal zone of the diencephalon (8 week embryo). *A* and *B* are pericapillary ameboid cells; *C* is a microglia cell in mitotic division; *D* and *E* are more mature forms, and *Cap* is a capillary. Silver carbonate stain.

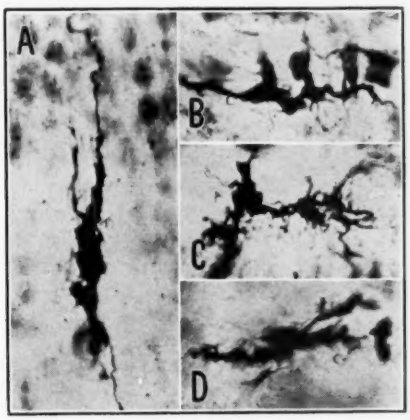


Fig. 6.—Photomicrographs of microglia cells in the cerebral hemispheres. *A* is from the cortical zone of a 16 week embryo; *B*, from the subcortical zone of a 27 week embryo; *C*, from the intermediary zone of a 23 week embryo, and *D*, from the subependymal zone of a 20 week embryo. Silver carbonate stain.

cortical and subcortical regions. With growth, the number of microglia cells in the cerebrum gradually increased, and they were soon seen scattered diffusely in all zones of the developing cerebrum (fig. 6).

Microglial Fountains in the Forebrain.—In addition to the isolated branched cells, certain areas containing nests of ameboid and migratory microglia cells were observed. Such collections of ameboid cells occurred constantly in the same locations during the whole period of embryonic development (fig. 7).

The earliest evidence of these nests in the forebrain was seen at 11 weeks. However, it is probable that they occurred even earlier. They were observed in the same locations at every subsequent age period.

In the anteromedial region of the dorsal part of the internal capsule, the brain is especially rich in capillaries. Around these capillaries there were a large number of ameboid cells (fig. 8). Pseudopodic microglia cells radiated into the surrounding brain, and elongated microglia cells with expansions ran between the fibers of the internal capsule. At the margins of the internal capsule some of the ameboid cells were in close contact with the peripheral expansions of spongioblasts (fig. 9), and these microglia cells, as well as the neighboring ones, contained granular débris and fat. They were apparently carrying on phagocytic activity. The spongioblasts themselves were noteworthy. Their expansions were granular and much more beaded than normal; many of them were obviously fragmented.

Laterally, in the region where the external and the internal capsule meet, a similar perivascular herd of microglia cells was present (fig. 7 *E.C.*).

A large focus of granular ameboid microglia cells containing fat was observed around the vena terminalis (fig. 7 *V. t.*). Radiating from this zone into the brain there were again observed pseudopodic and branched microglia cells. Such a constellation of microglia forms was typical of all the nests.

Within the core of the choroid plexuses of the third and lateral ventricles a large number of ameboid, fat-containing cells was seen, and at the points where the choroid plexuses were attached to the brain there was a continuous stream of such cells, a group of them lying in the cerebral tissue (fig. 7 *Ch. pl.*). Thus, clusters of ameboid microglia cells lay on the ventricular aspect of the fornix and crowded into the corpus callosum immediately above it; similar groups occurred in the superior border of the thalamus and in the caudate nucleus adjacent to the attachments of the choroid plexus, superiorly and inferiorly. More deeply, among the caudate cells and in the thalamus only complexly branched microglia cells occurred.

In the 14 week embryo aggregations of ameboid microglia cells appeared around the cerebral peduncles and optic tracts in the region where they join the forebrain (fig. 7 *I. C.* and *O. T.*). Smaller groups occurred just under the meninges lining the lower border of the neighboring portion of the diencephalon, accompanying blood vessels which penetrated the brain in this region. Simultaneously, ameboid cells, morphologically identical with microglia cells, were stained in the overlying meninges.

At this age, also, a small nest made its appearance in the outer (submeningeal) aspect of the corpus callosum, under the reflection of the falx. At the 16 week stage this group of ameboid microglia cells was much larger, so that now they occurred on both the outer and the inner (ventricular) aspect of the corpus callosum. The aggregation in the latter region soon spread along the subependymal region of the neighboring portion of the brain (fig. 7) and gradually increased in size.

In man the rhinal fissure remains an embryonic structure, but rostrally it marks the region where the olfactory tracts join the brain. At this point a microglial fountain was always present (fig. 7 *4*). A similar nest was seen constantly in the hippocampal fissure (fig. 7 *1*). In this region a great many

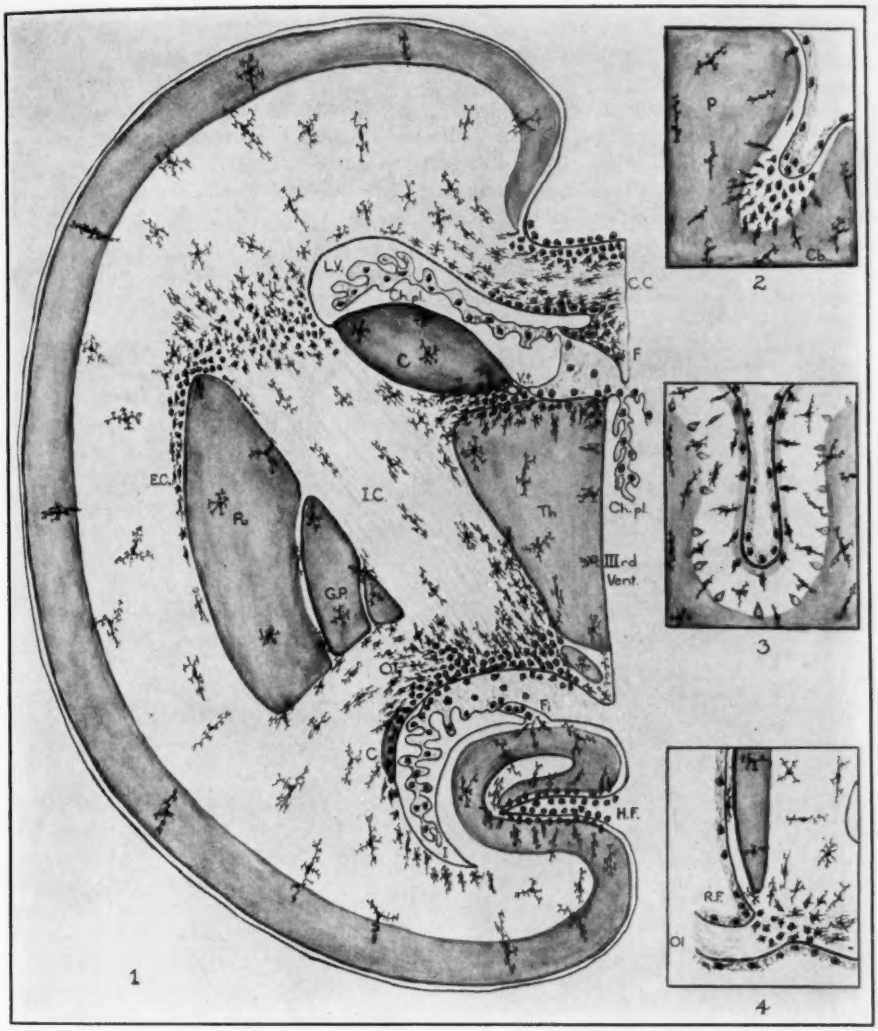


Fig. 7.—Diagrams showing microglial fountains during development.

1 represents a frontal hemisection of the brain of an embryo at about the 25 week stage. The age is approximate, and the diagram illustrates the location of all the microglial fountains which persistently occur throughout embryonic life. *C* indicates the caudate nucleus; *C. C.*, the corpus callosum; *Ch. pl.*, the choroid plexus; *E. C.*, the external capsule; *F*, the fornix; *Fi*, the fimbria; *G. P.*, the globus pallidus; *H. F.*, the hippocampal fissure; *I*, the inferior horn of the lateral ventricle; *I. C.*, the internal capsule; *L. V.*, the lateral ventricle; *O. T.*, the optic tract; *Pu*, the putamen; *Th*, the thalamus; *V. t.*, the vena terminalis, and *IIIrd Vent.*, the third ventricle.

At the fountains the microglia cells are ameboid; more peripherally they are branched. Similar ameboid cells are shown in the choroid plexuses, over the corpus callosum and in the hippocampal fissure.

2 shows the rhombic furrow between the pons (*P*) and the cerebellum (*Cb.*) in an 8 week embryo; *3*, the surface of the cerebellum, and *4*, the region of the rhinal fissure (*R. F.*). *Ol* indicates the olfactory tract. In *2*, *3* and *4* the meningeal lining is indicated and contains ameboid cells which are identical with ameboid microglia cells in the fountains.

extracerebral meningeal ameboid cells were observed, the morphologic character of which was similar to the intracerebral marginal ameboid microglia cells (fig. 10).

In the 29 week fetus all the microglial nests previously described were still present (fig. 11). In addition, a constantly increasing number of stable, branched microglia forms was gradually accumulating in all the zones of the developing brain.

From the 29 week stage till birth, it was difficult to obtain brains in a sufficiently normal state to warrant any conclusions. In this period the usual cause of death

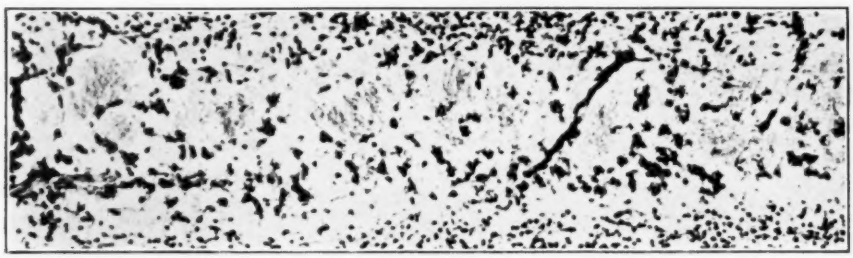


Fig. 8.—Photomicrograph of perivascular herds of ameboid microglia cells in the internal capsule of an 11 week embryo. Silver carbonate stain.

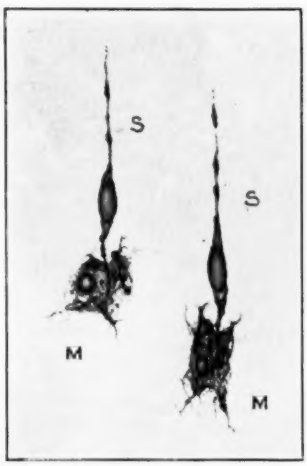


Fig. 9.—Drawing of ameboid microglia cells (*M*), containing granular débris, surrounding the expansions of spongioblasts (*S*) in an 11 week embryo. The spongioblastic expansions are thickened, granular, beaded and fragmented. Silver carbonate stain.

is trauma at birth or eclampsia. Both these conditions, especially the former, cause marked pathologic alterations in the brain; as a result, microglia cells are mobilized rapidly. It is impossible to distinguish between the phagocytic mobile microglia cells occurring in response to pathologic processes and the ameboid microglia cells constantly seen during normal development.

The striking regularity with which these microglial nests were observed in every embryo and in the same locations proves that they are of normal occurrence. The fact that stable, branched microglia cells constantly increased in number and could be traced by numerous morphologic transformations from these nests indicates that the latter act as fountains from which microglia cells are constantly projected into the brain. In addition to these major fountains, there were smaller, ubiquitous foci where isolated ameboid perivascular cells and submeningeal ameboid elements developed into mature branched microglia cells.

Specific staining methods easily distinguished microglia cells from spongioblasts and neuroblasts in the hemispheral wall. No less important is the fact that even when all the cells were stained with silver carbonate, microglia cells could easily be distinguished by morphologic criteria (fig. 12). Microglia cells are more

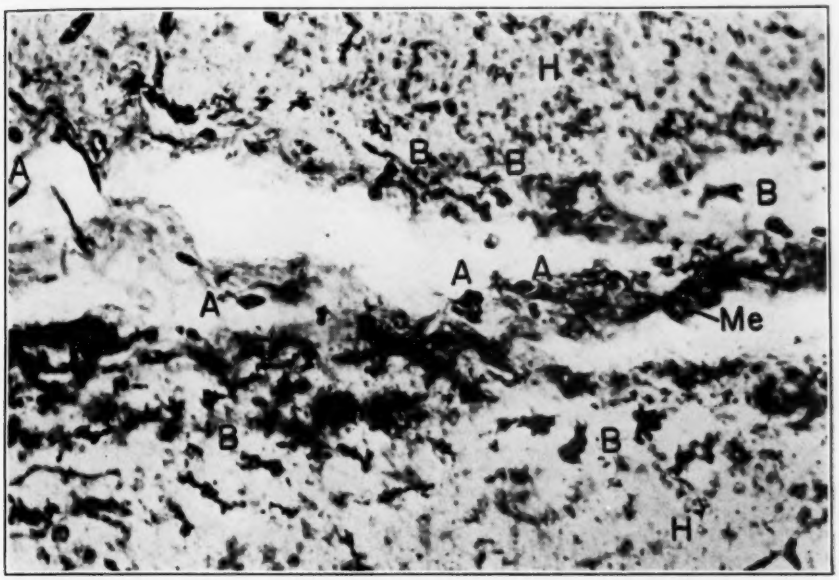


Fig. 10.—Photomicrograph from the region of the hippocampal fissure in a 27 week embryo. *A* indicates ameboid mesenchymal cells; *B*, microglia cells; *H*, the hippocampus, and *Me*, the meninges. Many transitional forms between these cells can be observed. Silver carbonate stain.

irregular and their nuclei more densely staining and varied in shape, and their cytoplasm is more granular and uneven, with polymorphic expansions.

There were many obvious transitional forms between ependymal cells and apolar and polar spongioblasts. Development of the spongioblasts into oligodendroglia cells and astrocytes could readily be traced (Kershman, 1938), but at no stage did these cell forms show any morphologic transitions to microglia cells.

In addition to the extracerebral ameboid cells in the meninges and those in the choroid plexuses which were identical with the ameboid forms of intracerebral microglia, it was possible with the same technic to demonstrate similar cells in the muscles of the embryonic heart and tongue. These cells were the histiocytes

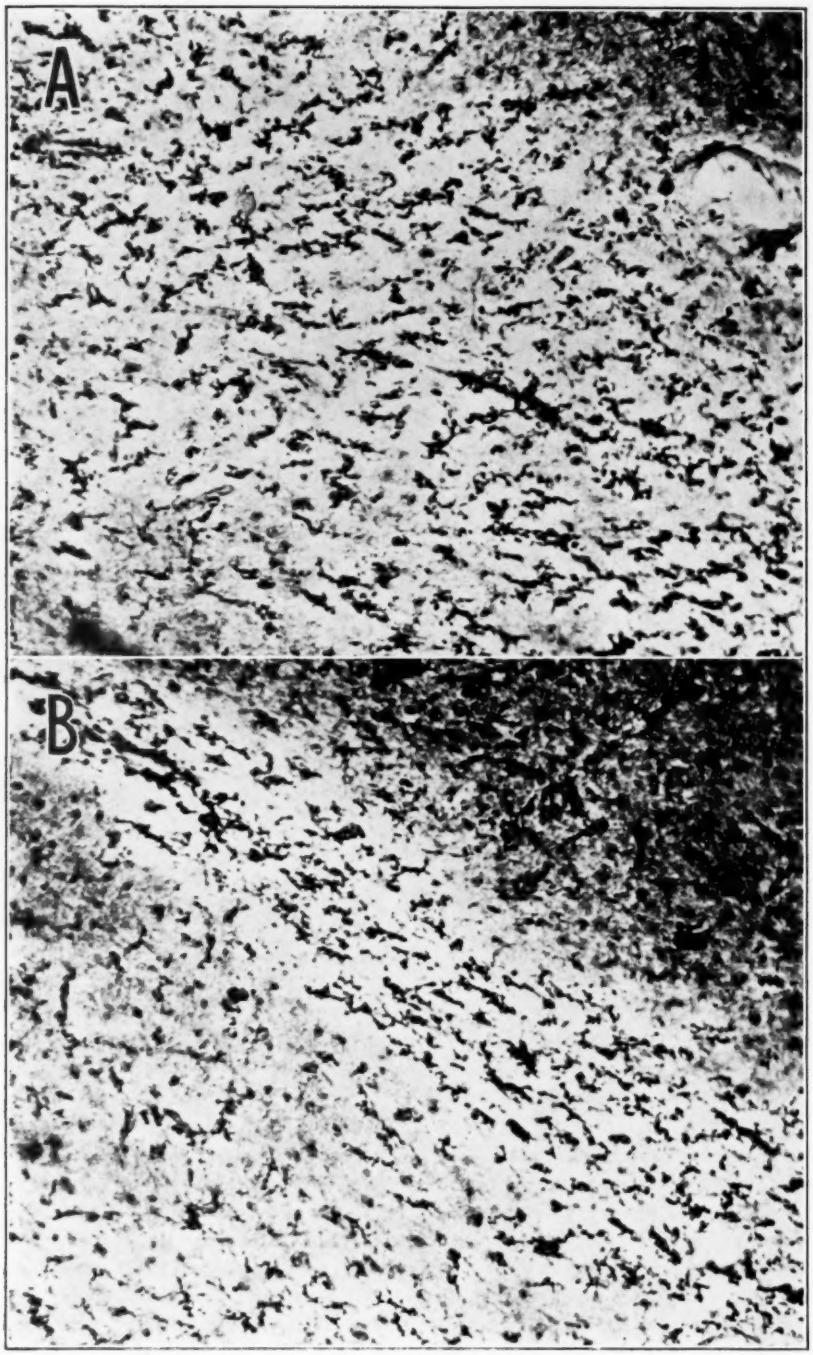


Fig. 11.—Photomicrographs of microglial fountains in a 27 week embryo. *A* shows a nest around the internal capsule, and *B*, a nest around the optic tract. Silver carbonate stain.

of these tissues, and their close morphologic relationship to microglia cells has already repeatedly been pointed out (Cone, 1928; Hortega, 1932; Dunning and Stevenson, 1934).

Earliest Appearance of Microglia.—In view of the fact that microglia cells were already present in the youngest embryo of this series (8 weeks) and no transitional forms were seen relating them to the neural ectoderm, a number of younger specimens were examined to see if any more information could be obtained regarding the origin of these cells.

All the specimens [2] from which any critical conclusions were drawn had been freshly fixed and stained with hematoxylin and eosin or similar dyes. No specific impregnations for microglia were available.

Up to the 4 mm. stage, the neural wall of the human embryo was composed of multilayered columnar epithelium with little evidence of a mantle zone and only a very thin marginal zone. No blood vessels were present within the neural tube, which was loosely surrounded by mesenchymal tissue.

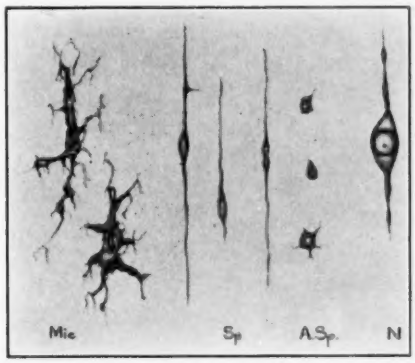


Fig. 12.—Drawing of cell types in the cerebral hemisphere. *Mic* indicates microglia cells; *Sp*, spongioblasts; *A. Sp.*, apolar spongioblasts, and *N*, a neuroblast. Silver carbonate stain.

Formation of the primitive meninges occurred shortly after (at about the 5 mm. stage) by the closer accumulation of some of the cells surrounding the neural wall. At about the same time certain peripheral cells within the neural wall lost their parallel periependymal orientation and began to form a definite mantle zone. This phenomenon was first seen in the rhombencephalon and cervical part of the spinal cord.

After this, the first blood vessels appeared within the neural wall. This occurred in the basal plate of the rhombencephalon of the 5.8 mm. embryo. The first evidence was a capillary-like structure in the marginal zone continuous with a similar embryonic vascular channel in the overlying primitive meninges (fig. 13*a*). Within the neural wall this structure consisted of a row of elongated cells, forming at first a solid column and then a hollow channel, within which were embryonic

2. These embryos are part of the excellent collection at the Carnegie Institute of Embryology, Baltimore. Dr. G. L. Streeter, director, granted me permission to study them.

blood cells. Many of the cells were in mitotic division. At this time a definite mantle zone was present in the neural wall, formed by neuroblasts the processes of which passed into the marginal zone.

When the first vascular sprout was seen, an irregular cell with a flattened angular nucleus appeared in the marginal zone, near the same region, just under the external limiting membrane (fig. 13 *b*). This cell obviously differed morphologically from the neuroectodermal elements, but closely resembled some of the cells in the overlying mesenchyme. The cytoplasm stained faintly and appeared to be ameboid and pseudopodic. The cell bore a striking resemblance to the mobile forms of microglia identified by Hortega's stain in the marginal zone of the 8 week embryo.

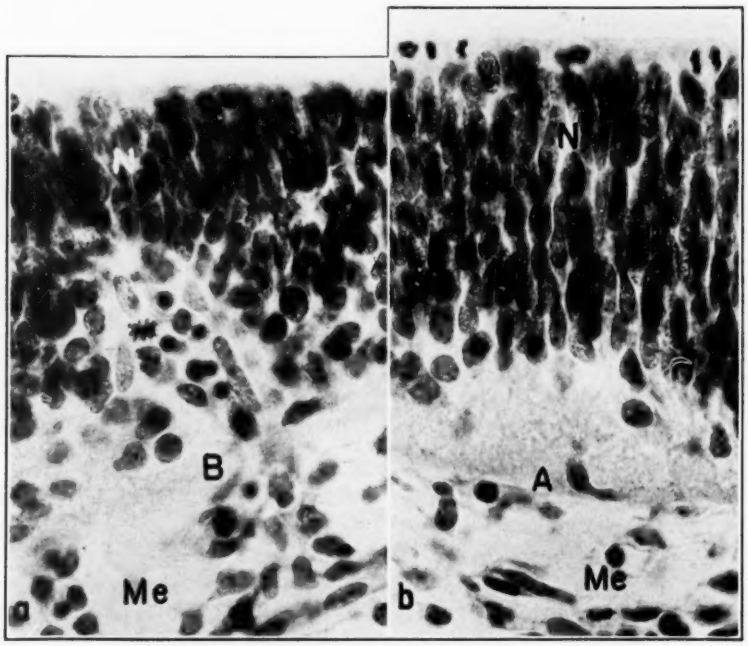


Fig. 13.—Photomicrographs from the basal plate of the rhombencephalon in a 5.8 mm. embryo. Here, *a* represents the first vascular sprout in the neural wall; *b*, an adjacent area, showing the first microglia-like cell in the marginal zone; *A*, an ameboid cell in the marginal zone, just under the meninges; *B*, a blood vessel; *Me*, the meninges, and *N*, the wall of the neural tube. Hematoxylin and eosin stain. Carnegie collection, no. 6503.

From the 5.8 mm. embryo there was a gradual increase in vascularization, the process spreading rostrad and caudad from its initial location. Accompanying this was a gradual increase in the isolated irregular cells in the marginal zone (fig. 14). In the 25 mm. (8 week) embryo these cells in the marginal zone could be definitely identified as microglia forms by the silver carbonate stain.

During this period another suggestive phenomenon occurred. After the first intracerebral vascular sprout appeared, a number of spherical cells were seen

lying loose in the neural wall (fig. 14). They were not confined by any capillary wall, though they appeared at first only around the latter. Later, they were freely dispersed among neuroectodermal cells and were often in mitotic division. Morphologically, they were similar to intracapillary hemangioblasts, and, though special blood stains were not available, were obviously blood forming cells. That their occurrence was not fortuitous was seen from the fact that they appeared in every embryo up to 19 mm. After this age they were rare, but with their disappearance cells which could be identified as microglia cells were seen lying ubiquitously throughout the neural wall (25 mm. embryo).

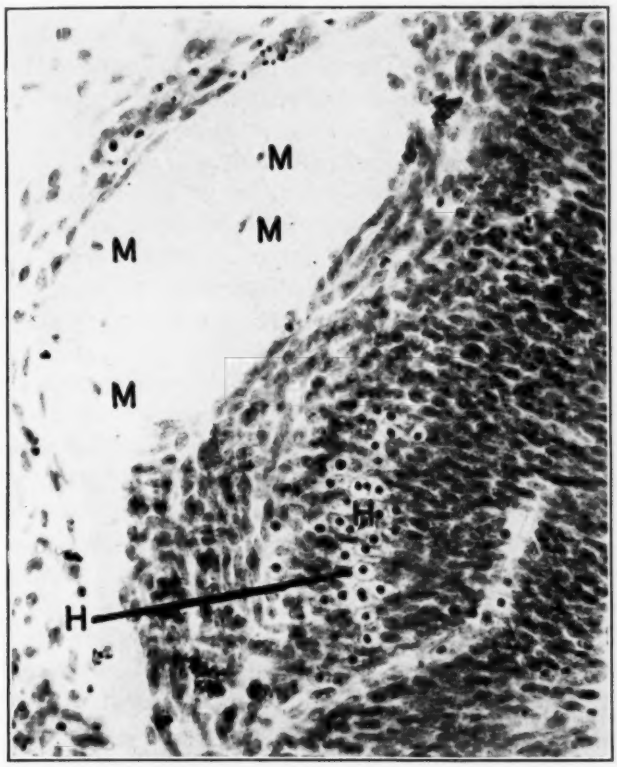


Fig. 14.—Photomicrograph from the posterolateral segment of the spinal cord in a 12 mm. embryo. *H* indicates hemangioblastic cells freely dispersed between neuroectodermal elements, and *M*, cells in the marginal zone which in older (8 week) embryos were identified as microglia elements. Hematoxylin and eosin stain. Carnegie collection, no. 6521.

COMMENT

In the present study, by means of Hortega's silver carbonate stain and various modifications, microglia cells were identified in a series of embryos from the age of 2 months. Indeed, on morphologic grounds, it was thought that microglia cells can be identified at an even earlier age (5.8 mm. embryo), and their earliest appearance seemed to occur simultaneously with that of intracerebral blood vessels.

Many different forms of microglia cells were observed, from the ameboid to the complexly branched type. At no time during embryonic life was there evidence of transitional forms to suggest that microglia in any of its developmental stages is derived from neuroectodermal ependymal elements.

It has been suggested by Pruijs that *Stäbchenzellen,* or rod-shaped cells, occur in the subependymal zone of the developing rabbit cerebrum which are derived from the ependyma and become transformed into microglia cells. Rydberg reported similar observations in human fetuses and newborn infants, as well as in rabbits.

Because of this, the brains of a number of rabbit embryos were examined, as well as those of the human embryos reported on here. With specific stains for microglia I observed few "rod forms" of microglia in the subependymal zone of these embryos. It was obvious, however, that when the silver stains were not specific in staining microglia elements many other cell forms, especially spongioblasts, could be demonstrated. Throughout embryonic development there were a tremendous number of elongated polar spongioblasts (fig. 12 *Sp.*) in the subependymal and intermediary zones. Their nuclei were elongated and sometimes serrated, and the cell bodies were elongated and narrow. These cells bore only a superficial resemblance to the rod-shaped microglia cell, and when their further development was studied it became obvious that they gave rise exclusively to neuroglia (Kershman, 1938). Confusion existed only when inadequate staining methods were employed and when the later evolution of these elongated spongioblasts was not examined critically. Juba (1933) reached similar conclusions regarding Pruijs's rod cells.

The same lack of differential staining was responsible for Rydberg's conclusions that ameboid cells are derived from ependyma and may give rise to astrocytes and oligodendroglia cells as well as to microglia cells. His reference to "naked nuclei" as one of the intermediary forms in the development of all these cells testifies to the inadequacy of his staining methods. The concept of the existence of "naked nuclei" has been universally discarded since the metallic stains were introduced, and it has been generally agreed that their appearance is an artefact resulting from incomplete cell staining. Personal observations on human and other embryos demonstrated conclusively, as in the adult, that when staining is complete there are no "naked nuclei" in the developing brain.

Rydberg's contention that ameboid cells may develop into astrocytes and microglia cells is reminiscent of the confusion that existed several years ago, before it was finally proved that the ameboid forms of microglia and the "ameboid glia" cells resulting from degenerated astrocytes are entirely different in origin and significance (Penfield, 1925; Penfield and Cone, 1926, and Cone, 1928). It is only when non-

specific stains are employed that a superficial morphologic resemblance seems to be present. That Rydberg fell into this old misconception seems more probable in view of the fact that many of his observations were made on the brains of infants who succumbed after severe birth trauma, in which there was the likelihood of astrocytic degeneration to complicate the picture of normal histogenesis.

In the present material there was no evidence that ameboid cells are an intermediary stage in the development of normal astrocytes or oligodendroglia cells. This is corroborated by almost every other investigator of the genesis of neuroglia.

Repeated reference has been made to the various forms of microglia cells that were observed in the human embryos in this series. The genetic unity of these cells, as shown by the numerous transitional forms, was corroborated by the specificity of their response to selective staining methods. These microglia cells were identical with the forms observed in mammalian fetuses by Hortega, Penfield, Bolsi, Gozzano and Santha and Juba. In tissue cultures of microglia cells these various transformations between the ameboid and the branched microglia cell have been observed directly.

In fixed sections it is admittedly difficult to establish with certainty the direction in which migration and transformation of cells occur. From work with tissue cultures, however, it is definitely known that the ameboid and pseudopodic forms of microglia are the mobile cells, while the branched cells are stable. In younger embryos (2 months) the mobile forms far outnumber the branched microglia cells. Gradually, the latter increase in number, and in structures such as the spinal cord and brain stem it was possible to correlate this increase with the final disappearance of ameboid microglia cells. In the cerebrum and cerebellum, though ameboid cells did not disappear until after birth, there was also a gradual, constant increase in stable microglia cells during embryonic development.

The first branched, stable microglia cells occurred only at the periphery of the microglial fountains. With growth, more stable forms appeared in a wider peripheral zone. It seems reasonably certain, therefore, that the migration of microglia cells is inward to the cerebral tissue and that the stable forms originate from ameboid microglia cells.

During pathologic processes (Hortega, 1932; Penfield, 1928) a complete reversal of the direction of migration takes place, with the cellular transformations also in the opposite direction.

The Specific Precursor of Microglia.—The youngest forms of microglia were constantly observed in intimate relation to blood vessels, attachments of the choroid plexuses and meninges. The nests of ameboid elements from which the greatest number of microglia cells originated were always in close proximity to mesenchymal tissue. In the neighbor-

ing meninges and in the choroid plexuses, ameboid and pseudopodic cells, often containing fat droplets, were repeatedly demonstrated simultaneously with intracerebral microglia cells by the silver carbonate technic. These ameboid cells were morphologically indistinguishable from ameboid microglia elements, and in many areas (figs. 7 and 10) it was possible to stain a continuous stream of such cells passing from the meninges and choroid plexuses into the cerebral tissue. In the mesenchymal tissues these migratory cells, because of their granular, fat-containing, ameboid character, were undoubtedly histiocytes. Similar cells were stained in muscle with the silver carbonate method.

In very young embryos (5.8 mm.) it was possible without special stains to identify cells in the marginal zone of the neural wall which had no apparent genetic relation to the neuroectoderm and which closely resembled mesenchymal elements. This occurred coincidentally with the first penetration of intraneural vascular channels. For a short time after, a number of free hemangioblastic elements were observed among the neuroectodermal cells in the wall of the neural tube. These were probably derived from wandering mesenchymal cells, which at this early age have almost unrestricted potentiality (Maximow and Bloom, 1930). Later, their potentialities become limited, and they give rise exclusively to microglia.

From these observations, therefore, it must be concluded that microglia cells are derived from embryonic mesenchymal cells. These mesenchymal cells are identical with the elements which become histiocytes in the meninges and other tissues.

That microglia cells are the histiocytes of the brain has been repeatedly suggested by a number of observers. Hortega, who inclined to this view, summarized the evidence in 1932. Further work substantiating this conclusion has appeared since. Lazarenko (1931) and Mihálik (1932) observed histiocytes growing in tissue cultures of the brains of chick embryos in from three to twenty days of incubation; Mihálik, on the basis of this work, concluded that if these cells are derived from microglia they must be present in the brain much before the time of birth suggested by Hortega. Belezky (1932) demonstrated microglia cells in chick embryos at these early ages, and Dunning and Furth (1935) showed the similarity between the microglia cells from the brains of the embryo chick and guinea pig and the histiocytes from the kidney.

Santha and Juba were the first to demonstrate microglia cells in the brains of very early rat embryos. They expressed the belief that microglia cells appear at the time of vascularization and that monocytes from the circulating blood may give rise to them, in addition to wandering mesenchymal elements. Juba, in his study of microglia in human embryos, also advanced this view.

In the present study many microglia cells were seen to originate around blood vessels, but it was thought that they are derived from perivascular histiocytes rather than from circulating elements in the blood stream, though the latter cannot be excluded. In view of opinions regarding the origin and potentialities of monocytes, the derivation of microglia from them cannot be denied.

In all important particulars, the present observations are a confirmation and elaboration of Juba's work on the genesis of microglia in human embryos. It has now been possible to demonstrate the exact mesenchymal precursor from which microglia cells originate and to show that, as in rats, these cells occur in the human brain with the first evidence of vascularization.

One further point needs to be discussed. Harvey and Burr (1926) and Harvey, Burr and Van Campenhout (1933) concluded, as the result of experimental work, that in Amblystoma at least part of the pia-arachnoid is derived from the neural crest. This was cited by Ariëns Kappers (1929) and Rydberg as evidence that even if ameboid cells migrate inward from the pia to form microglia, both are of ectodermal origin. Flexner (1929), after repeating the work of Harvey and Burr, concluded that there was no reason for accepting their hypothesis; there is no evidence to indicate that what may be true in Amblystoma is necessarily so in higher animals and in man. It has, moreover, never been demonstrated that the specific histiocytic elements in the meninges are derived from the neural crest, and it is precisely these cells which in the present study were seen to give rise to microglia.

The present trend in embryology to minimize the importance of the formal division of embryonic cells into ectoderm, mesoderm and entoderm will doubtless lead to a less diagrammatic and more fluid conception of cellular differentiation. However, the evidence with regard to the origin of microglia cells shows that they are not derived from neuroectodermal ependymal elements, like neuroglia; they come from a different source. The embryonic derivation of microglia cells from embryonic mesenchymal wandering cells confirms the genetic unity of microglia cells with the other elements of the reticuloendothelial system.

Significance of Microglial Nests.—A remarkable feature of microglial fountains is their constant occurrence in relation to tract zones (fig. 7). Penfield (1928) pointed out that they occur in the only three areas of the brain in which the pia mater comes into close contact with the white matter. In addition in the human embryo nests were seen to be situated elsewhere about blood vessels within the brain, but nearly always in tract zones. In the 25 mm. embryo a nest was observed in the posterolateral angle of the spinal cord at an age when fibers are accumulating here to form the posterior column. In the

hindbrain a nest was observed at the site of formation of the cerebellar peduncles. Later, significant nests were observed at the margins of the internal capsule, in the fornix and corpus callosum, around the optic tracts and in the rhinal fissure where the olfactory tracts join the brain. From these areas pseudopodic cells streamed into the brain, usually following the direction of tract formation.

The constancy with which this occurs invites an explanation. It has been suggested that the process of myelination in tract areas has a chemotactic influence on mesenchymal cells, causing them to migrate inward and carry in fat, which contributes to the formation of myelin. However, no myelin occurs in the posterior columns until the third month, at the earliest, and none can be observed cephalad to the midbrain until after the sixth month (Keene and Hewer, 1931; Langworthy, 1932, and personal observations). In these human embryos, therefore, microglial nests were observed in tract zones long before myelination. Although later participation of microglia cannot be entirely excluded, my observations suggest that oligodendroglia rather than microglia cells are the elements cooperation of which is important for formation of myelin in the central nervous system.

The possibility, however, suggests itself that microglia cells may be attracted into the brain by certain conditions accompanying the formation of tract pathways. The earliest microglia cells in the spinal cord and hindbrain were in the marginal zone, where the nerve fibers accumulate to form tracts. In the internal capsule ameboid microglia cells were seen at the borders and were often attached to the fragmented peripheral expansions of spongioblasts (fig. 9). The latter cells had long peripheral expansions, which must necessarily be displaced or rearranged by the ingrowth of tracts. Similar changes occur when spongioblasts develop into the more complex astrocytes, a phenomenon which occurs earliest and most rapidly in tract zones. Microglia cells appeared to play an important role in this rearrangement, and the breakdown of spongioblastic processes may be an important stimulus that causes an influx into tract areas of macrophagic histiocytes, which later form microglia cells.

In a study of the differentiation of nerves, Grigorjeff (1931) produced growths in culture of pieces of nerve tissue, together with heart mesenchyma, and watched the relation between the two. He found that the mesenchymal cells gave direction to the growing fibers and that, as a result of attraction exerted by the mesenchymal elements, the nerve fibers often changed their direction, sent out branches, and the like. Thus, he concluded that mesenchyma is of great importance in the differentiation of neuroblasts in culture and that there seems to be a striking neurotropic effect of mesenchyma on the growth and differentiation of nerve processes.

In view of the curious and constant relationship between tract pathways and the mesenchymal migratory microglia elements, Grigorjeff's ideas may be pertinent in explaining the direction of growth of nerve fibers in the central nervous system. For example, in the internal capsule and the corpus callosum, it is obvious that the migratory forms of microglia spread through the brain in the same direction as that in which growth of the tract occurs. However, the rearrangement of spongioblasts already referred to and the formation of tracts occur synchronously, and microglia may have an important function in both these processes. Further work is needed to substantiate this hypothesis.

A few words are necessary with regard to Virchow's congenital encephalitis. For a long time the existence of this syndrome was accepted because of the occurrence of fat-laden cells in the brains of newborn infants. Before the description of microglia, however, Hayem, Jastrowitz, Merzbacher (1909) and others expressed the belief that the existence of fat-containing granular cells in human embryos is normal, and not necessarily the result of an inflammatory process. After Hortega's description of the origin of microglia, the nature of these cells in embryos was clarified. The present study confirms the fact that the existence of fat-laden ameboid cells in the brain during development is normal.

SUMMARY AND CONCLUSIONS

1. Twenty-two normal human embryos and fetuses, ranging from 8 to 29 weeks in age, were examined for microglia by silver carbonate methods.

2. Microglia cells were observed in the brain and spinal cord of all these specimens.

3. The youngest forms of microglia were ameboid elements, often containing fat droplets and granular inclusions. They migrated into the brain mainly from certain constant locations, which may be called fountains.

4. These fountains occurred at points where the choroid plexuses were attached to the brain, around certain large blood vessels in tract areas and beneath the meninges where the latter came in contact with tracts.

5. Within the choroid plexuses and in the meninges the precursors of microglia cells were embryonic wandering mesenchymal elements—the histiocytes of these tissues. Similar cells could be stained in other organs by the technic for microglia.

6. After invading the central nervous system as ameboid forms, microglia cells gradually became pseudopodic and, as they penetrated more deeply, developed by gradual transitions into more complexly

branched forms. On reaching their final location, they ultimately assumed the shape of normal stable microglia cells.

7. Although no specific stains could be used for confirmation, the first evidence of microglia was observed in the basal plate of the rhombencephalon in a 5.8 mm. embryo. This occurred at the same time and in the same location as the earliest blood vessels within the central nervous system.

8. The constant association of microglial fountains and areas of tract formation suggests the likelihood of an important functional correlation. Two possibilities were discussed. There was no evidence that microglia played any role in the process of myelination.

9. There is no genetic relation between microglia and neuroglia (astrocytes and oligodendroglia cells). The neuroglia is derived from the cells lining the wall of the neural canal. Microglia is of mesenchymal origin and is related to the reticuloendothelial system.

Prof. Wilder Penfield and Assoc. Prof. William Cone gave advice and stimulating criticism during the course of this study.

BIBLIOGRAPHY

Ariëns Kappers, C. U.: The Evolution of the Nervous System in Invertebrates, Vertebrates and Man, Haarlem, Netherlands, de Erven F. Bohn, 1929.

Belezky, W. K.: Ueber die Histogenese der Mesoglia, Virchows Arch. f. path. Anat. **284**:295, 1932.

Bolsi, D.: Il problema della origine della microglia, Riv. di pat. nerv. **48**:1, 1936.

Cone, W. V.: Acute Pathologic Changes in Neuroglia and Microglia, Arch. Neurol. & Psychiat. **20**:34 (July) 1928.

Costero, I.: Experimenteller Nachweis der morphologischen und functionellen Eigenschaften und des mesodermischen Charakters der Mikroglia, Ztschr. f. d. ges. Neurol. u. Psychiat. **132**:371, 1931.

Dunning, A. S., and Furth, J.: Studies in the Relation Between Microglia, Histiocytes and Monocytes, Am. J. Path. **11**:895, 1935.

——and Stevenson, L.: Microglia-Like Cells and Their Reaction Following Injury to the Liver, Spleen and Kidney, ibid. **10**:343, 1934.

Flexner, L. B., cited by Weed.

Gozzano, M.: Quelques observations sur l'origine de la microglie, Rev. neurol. **1**:1024, 1930.

L'istogenesi della microglia, Riv. di neurol. **4**:3, 1931.

Grigorjeff, L. M.: Differenzierung des Nervengewebes ausserhalb des Organismus, Arch. f. exper. Zellforsch. **11**:483, 1931.

Harvey, S. C., and Burr, H. S.: The Development of the Meninges, Arch. Neurol. & Psychiat. **15**:545 (May) 1926.

——Burr, H. S., and Van Campenhout, E.: Development of the Meninges, ibid. **29**:683 (April) 1933.

His, W.: Die Entwicklung des menschlichen Gehirn, Leipzig, S. Hirzel, 1904.

Jacob, A.: Das Kleinhirn, in von Möllendorff, W. V.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1928, vol. 4, p. 674.

Juba, A.: Untersuchungen über die Entwicklung der Hortegaschen Mikroglia des Menschen, Arch. f. Psychiat. **101**:577, 1933.

Keene, M., and Hewer, E.: Some Observations on Myelinization in Human Central Nervous System, J. Anat. **66**:1, 1931.

Kershman, J.: The Medulloblast and the Medulloblastoma: A Study of Human Embryos, Arch. Neurol. & Psychiat. **40**:937 (Nov.) 1938.

Langworthy, O.: Development of Behavior Patterns and Myelinization of Tracts in Nervous System, Arch. Neurol. & Psychiat. **28**:1365 (Dec.) 1932.

Lazarenko, T.: Ein Beitrag zur Morphologie des Wachstums vom embryonalen Nervengewebe in vitro, Arch. f. exper. Zellforsch. **11**:555, 1931.

Marinesco, G., and Minea, I.: Die Kultur des Gliagewebes der Grosshirnrinde in vitro Angaben zur Bildung und Funktion der amöboiden Zellen, Zentralbl. f. d. ges. Neurol. u. Psychiat. **41**:137, 1925.

Contribution à l'étude de la culture in vitro de la névroglie et de la microglie, Rev. neurol. **1**:994, 1930.

Maximow, A. A., and Bloom, W.: A Textbook of Histology, Philadelphia, W. B. Saunders Company, 1930.

Merzbacher, L.: Untersuchungen über die Morphologie und Biologie der Abraumzellen in Zentralnervensystem, in Nissl, F., and Alzheimer, A.: Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten, Jena, Gustav Fischer, 1909-1910.

Mihálik, P.: Macrophages in Cultures of Chick Embryo Brain, Anat. Rec. **54**: 157, 1932.

Penfield, W. G.: Microglia and the Process of Phagocytosis in Gliomas, Am. J. Path. **1**:77, 1925.

A Method of Staining Oligodendroglia and Microglia (Combined Method), ibid. **4**:153, 1928.

Neuroglia and Microglia: The Interstitial Tissues of the Central Nervous System, in Cowdry, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1928, vol. 2, p. 1032.

Neuroglia, Normal and Pathological, in Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 423.

——and Cone, W. V.: The Acute Regressive Changes of Neuroglia, J. f. Psychol. u. Neurol. **34**:204, 1926.

Neuroglia and Microglia (the Metallic Methods), in McClung, C. E.: Handbook of Microscopical Technique, New York, Paul B. Hoeber, Inc., 1928, p. 359.

Pruijs, W. M.: Ueber Microglia, ihre Herkunft, Funktion und ihr Verhältnis zu anderen Gliaelementen, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:298, 1927.

del Río Hortega, P.: Noticia de un nuevo y fácil método para la coloración de la neuroglia y del tejido conjuntivo, Trab. d. lab. de invest. biol. Univ. de Madrid **15**:1, 1918.

El tercer elemento de los centros nerviosos, Bol. Soc. espań. de biol. **9**:69, 1919.

La microglia y su transformación en células en bastoncito y cuerpos granuloadiposos, Trab. d. lab. de invest. biol. Univ. de Madrid **18**:37, 1920.

Histogénesis y evolución normal; éxodo y distribución regional de la microglia, Mem. R. Soc. espań. d. hist. nat. **11**:213, 1921.

Concepts histogénetique, morphologique, physiologique, et physio-pathologique de la microglie, Rev. neurol. **1**:956, 1930.

Microglia, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 483.

——and Jiménez de Asúa, F.: Sobre la fagocitosis en los tumores y en otros procesos patológicos, Arch. cardiol. y hemat. **2**:161, 1921.

Rydberg, E.: Cerebral Injury in New-Born Children Consequent on Birth Trauma, with an Inquiry into the Normal and Pathological Anatomy of the Neuroglia, Acta path. et microbiol. Scandinav., 1932, supp. 10, p. 1.

Streeter, G.: Development of the Central Nervous System, in Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 1.

Virchow, R.: Ueber das granulierte Aussehen der Wandungen der Gehirnventrikel, Allg. Ztschr. f. Psychiat. **3**:242, 1846.

Congenitale Encephalitis und Myelitis, Virchows Arch. f. path. Anat. **38**:129, 1867.

von Santha, K.: Untersuchungen über die Entwicklung der Hortegaschen Mikroglia, Arch. f. Psychiat. **96**:36, 1932.

——and Juba, A.: Weitere Untersuchungen über die Entwicklung der Hortegaschen Mikroglia, ibid. **98**:598, 1933.

Weed, L. H.: The Meninges, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 613.

Wells, A., and Carmichael, A. E.: Microglia: An Experimental Study by Means of Tissue Culture, Brain **53**:1, 1930.

THE HEMATOENCEPHALIC BARRIER

LESTER S. KING, M.D.
PRINCETON, N. J.

It has long been known that there are certain unusual features connected with the interchange of substances between the blood and the brain.

PREVIOUS INVESTIGATIONS

In 1900 Lewandowsky,[1] experimenting with sodium ferrocyanide, found a marked difference in the reaction of rabbits to this substance, depending on the mode of administration. If the chemical was introduced into the blood, even in fairly large quantities, no significant reactions were elicited, but if a minute quantity was placed directly into the cerebrospinal fluid, severe nervous disturbances with convulsions followed immediately, sometimes with lethal outcome. It seemed clear that material in the cerebrospinal fluid penetrates to the nerve cells with ease and that the nerve cells display a positive affinity for the ferrocyanide ion. Yet when the substance was introduced into the blood in doses from one to two hundred times greater than those injected in the cerebrospinal fluid, no nervous reactions were apparent. The conclusion was drawn that the capillary wall prevents the passage into the brain of certain substances, such as sodium ferrocyanide.

Similar experiments were performed by Goldmann[2] with the dye trypan blue. When this was injected into the blood stream no toxic symptoms resulted, but the entire body stained blue except the brain. Here, on the contrary, only the choroid plexus showed the dye; the brain tissue itself was colorless. On the other hand, if small doses were placed in the cerebrospinal fluid, marked symptoms resulted, and the nerve tissue was seen to be deeply stained at autopsy. Clearly, there was a mechanism at work preventing the passage of the dye from

---

Read before the Association for Research in Nervous and Mental Diseases, Dec. 27, 1937.

From the Department of Animal and Plant Pathology of the Rockefeller Institute for Medical Research.

1. Lewandowsky, M.: Zur Lehre von der Cerebrospinalflüssigkeit, Ztschr. f. klin. Med. **40**:480, 1900.

2. Goldmann, E. E.: Die äussere und innere Sekretion des gesunden und kranken Organismus im Lichte der "vitalen Färbung," Beitr. z. klin. Chir. **64**: 192, 1909; Experimentelle Untersuchungen über die Funktion der Plexus chorioideus und der Hirnhäute, Arch. f. klin. Chir. **101**:735, 1913; Vitalfärbung am Zentralnervensystem, Berlin, Georg Reimer, 1913.

the blood stream into the brain, a mechanism that did not apply to any other organ.

In the study of the relations between the blood and the brain and the problem of a barrier between them, trypan blue has been the substance most widely used. It is relatively nontoxic and easily visible in histologic preparations. Consequently, in this review I wish to pay special attention to the behavior of trypan blue.

When the dye was introduced by way of the blood stream, Goldmann, as has been stated, observed that in the nervous system only the choroid plexus (and the dura) stained with trypan blue. Subsequent workers have shown that this was not altogether correct. With an adequate dose and careful examination, granules of dye were demonstrated in the hypophysis,[3] tuber cinereum,[4] area postrema,[5] paraphysis,[6] pineal gland [7] and preoptic recess.[8] These are all highly specialized areas of tissue, not sharing the ordinary functions of the rest of the nerve parenchyma. In addition, however, dye was deposited to slight extent within the nerve tissue proper. With repeated doses of trypan blue granules were seen in perivascular macrophages and in microglia cells, especially in the brain stem around the central canal (and its caudal prolongation) and in the cornu ammonis.[9] Furthermore, certain cells in the leptomeninges stored the dye.[4] In the peripheral nerves, storage in the ectodermal Schwann cells, as well as the connective tissue elements, was demonstrated by Doinikow.[10] The presence of dye in the ganglia of the peripheral and the autonomic nervous system was especially studied by Tschetschujeva.[11]

---

3. Schulemann, W.: Beiträge zur Vitalfärbung, Arch. f. mikr. Anat. **79**: 223, 1912.

4. Rachmanow, A.: Beiträge zur vitalen Färbung des Zentralnervensystem, Folia neuro-biol. **7**:750, 1913.

5. Wislocki, G. B., and Putnam, T. J.: Note on the Anatomy of the Area Postrema, Anat. Rec. **19**:281, 1920.

6. Putnam, T. J.: The Intercolumnar Tubercle, an Undescribed Area in the Anterior Wall of the Third Ventricle, Bull. Johns Hopkins Hosp. **33**:181, 1922.

7. Biondi, G.: Studi sulla ghiandola pineale: III. I fenomeni secretori ed i lipoidi; i resultati della colorazione vitale alla Goldmann, Riv. ital. di neuropat. **9**:303, 1916.

8. Mandelstamm, M., and Krylow, L.: Vergleichende Untersuchungen über die Farbenspeicherung im Zentralnervensystem bei Injektionen der Farbe ins Blut und in den Liquor cerebrospinalis, Ztschr. f. d. ges. exper. Med. **58**:256, 1927.

9. Wells, A. Q., and Carmichael, E. A.: Microglia: An Experimental Study by Means of Tissue Culture and Vital Staining, Brain **53**:1, 1930. Mandelstamm and Krylow.[8]

10. Doinikow, B.: Histologische und histopathologische Untersuchungen am peripheren Nervensystem mittels vitaler Färbung, Folia neuro-biol. **7**:731, 1931.

11. Tschetschujeva, T.: Ueber die Speicherung von Trypanblau in Ganglien verschiedener Gebiete des Nervensystems, Ztschr. f. d. ges. exper. Med. **69**:208, 1930.

These loci of storage of dye in the nervous system are firmly established and have been repeatedly confirmed. It is significant, however, that these relationships apply to the normal adult animal. In the young, immature animal the relations are altered. Behnsen [12] was the first to show that in immature mice the nervous system stores trypan blue more extensively and intensively than in the adult animal. This property of immature tissue is rapidly lost, the storage of dye being less at the age of from 3 to 5 weeks than at that of from 1 to 2 weeks, and considerably less after the age of 5 weeks. In these young animals the areas of maximal storage correspond to the areas in the adult which also take up the dye; in the young, however, these regions stain more easily and deeply, and there is much dye elsewhere in the nervous system.

These observations in mice were confirmed in rabbits and cats by Penta,[13] who showed that the nervous system of neonatal animals contained more dye than that of the adult. Curiously, in the guinea pig this relation does not seem to hold. Stern and Peyrot [14] used sodium ferrocyanide as a test agent. They could not detect the substance in either the brain or the cerebrospinal fluid of neonatal guinea pigs, although it could be demonstrated with ease in neonatal rats, rabbits, cats and dogs. In these last species the positive reaction disappeared about the time when the eyes first opened. It has been pointed out that guinea pigs are born with their eyes open, evidence that their nervous system is more mature at birth than that of other animals. The passage of trypan blue or ferrocyanide into the brain of very young animals is obviously correlated inversely with the state of maturity of the nervous system. Confirmatory evidence on this problem is furnished by facts established in human pathologic conditions. It is well known that in conditions of jaundice in the newborn the brain may share the yellow coloration (*Kernicterus*) with the rest of the body; in the adult, on the other hand, even the most severe jaundice leaves the brain colorless. Bile pigments act toward the brain in a fashion similar to that of trypan blue or the ferrocyanide ion, and the human infant is comparable to the suckling mouse in the behavior of its brain toward such substances.

12. Behnsen, G.: Ueber die Farbsstoffspeicherung im Zentralnervensystem der weissen Maus in verschiedenen Alterzuständen, Ztschr. f. Zellforsch. u. mikr. Anat. **4**:515, 1927.

13. Penta, P.: Sulla colorazione vitale del sistema nervoso centrale negli animali, neonati, Riv. di neurol. **5**:62, 1932.

14. Stern, L., and Peyrot, R.: Le fonctionnement de la barrière hématoencéphalique aux divers stades de développement chez les diverses espèces animales, Compt. rend. Soc. de biol. **96**:1124, 1927.

When the nervous system is injured the storage relationships are altered. MacCurdy and Evans [15] first demonstrated vital staining in areas where the nerve tissue was affected by inflammation. This observation has been confirmed by innumerable investigators. Preeminent is the careful and excellent work of Macklin and Macklin,[16] who used stabs with a hot needle as the mechanism of injury. Among a host of other investigators along similar lines, McClellan and Goodpasture,[17] Siengalewicz,[18] Schmid [19] and Morgenstern and Birjukov [20] may be mentioned. Under conditions of injury the nerve tissue is colored blue macroscopically, and granules of dye are visible microscopically in many cells. With injury, in other words, the brain behaves like any other organ. The "barrier" is broken down.

A wide variety of noxious agents have been used at different times, but common to all is the fact that inflammation or necrosis is set up in the nervous system. All types of injury are not adequate to allow vital staining. I have shown elsewhere [21] that in two types of noninflammatory lesions, namely, axonal degeneration and wallerian degeneration, there is no increase in storage of dye in the affected parts of the nervous system. Alteration of the barrier, that is, storage of trypan blue in parts of the nervous system where it does not normally take place, is dependent on inflammatory or necrotizing changes. Other types of morphologic change are not sufficient to allow vital staining.

Significant facts with reference to vital staining of the nervous system were brought forward by Friedemann and Elkeles [22] and Wes-

15. MacCurdy, J. T., and Evans, H. M.: Experimentelle Läsionen des Centralnervensystems untersucht mit Hilfe der vitalen Färbung, Berl. klin. Wchnschr. **49**:1695, 1912.

16. Macklin, C. C., and Macklin, M. T.: A Study of Brain Repair in the Rat by Use of Trypan Blue, Arch. Neurol. & Psychiat. **3**:353 (April) 1920.

17. McClellan, R. H., and Goodpasture, E. W.: A Method for Demonstrating Experimental Gross Lesions of the Central Nervous System, J. M. Research **44**:201, 1923.

18. Siengalewicz, S. S.: The Action of Neo-Salvarsan and Carbon Monoxide on the Choroid Plexus and Meninges, J. Pharmacol. & Exper. Therap. **24**:289, 1924.

19. Schmid, H.: Beitrag zur Frage der "Bluthirnschranke," Arch. f. Psychiat. **95**:303, 1931.

20. Morgenstern, S., and Birjukov, M.: Weitere experimentelle Ergebnisse zur Frage der Permeabilität der Gehirncapillaren, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:640, 1928.

21. King, L. S.: (*a*) Vital Staining of the Nervous System: I. Factors in the Vital Staining of Neurones, J. Anat. **69**:177, 1936; (*b*) Vital Staining of Microglia, Arch. Path. **19**:656 (May) 1935.

22. Friedemann, U., and Elkeles, A.: Kann die Lehre von der Bluthirnschranke in ihrer heutigen Form aufrechterhalten werden? Deutsche med. Wchnschr. **57**:1934, 1931.

selkin.[23] It was shown that a number of basic dyes injected into the blood stream passed easily into the nerve tissue. On the other hand, a series of negatively charged dyes, of which trypan blue is an example, stained the brain little, or not at all. Wislocki and I,[24] confirming these data, showed further that many acid dyes and potassium ferrocyanide as well, acted like trypan blue in staining the hypothalamus selectively. In certain species of animals the area postrema was also colored. From the accumulated evidence, it appears that trypan blue is a prototype of a series of dyes which have in common an electronegative charge. Such dyes may stain specialized portions of the nervous system but leave the bulk of the parenchyma uncolored. Basic dyes as a class pass into the nervous system with great facility.

There are certain exceptions, such as safranin, which, although basic, are reported not to stain nerve tissue.[25] Certain amphoteric dyes, such as alizarin blue S, have an ambiguous behavior. Nevertheless, the weight of evidence makes it overwhelmingly probable that the charge of a dye is the determining factor which regulates its passage into nerve tissue. The chemical constitution, state of solution, size of particles and diffusibility in gelatin bear no correlation with the penetration of the test dye into the nervous system. Such penetration can be correlated only with the charge.

THEORETIC INTERPRETATIONS

With the aforementioned fundamental facts at one's disposal, certain theories concerned with the hematoencephalic barrier may now be examined. Much of the literature in the past fifteen years has been concerned with disproving the early theory of Stern and Gautier.[26] As this theory is now of historical importance only, the reader may consult Spatz [27] for a summary and criticisms. Stern and Gautier did not recognize the fundamental fact that the relationship of the blood and the cerebro-

23. Wesselkin, P. N.: Versuche über die Durchlässigkeit der Gefässe des Auges und Gehirns für saure und basische Farbstoffe, Ztschr. f. d. ges. exper. Med. **72**:90, 1930.

24. Wislocki, G. B., and King, L. S.: The Permeability of the Hypophysis and Hypothalamus to Vital Dyes, with a Study of the Hypophyseal Vascular Supply, Am. J. Anat. **58**:421, 1936.

25. Mandelstamm, M.: Beiträge zur vitalen Färbung des Zentralnervensystems mit basischen Farben: I. Einleitende Untersuchungen, Ztschr. f. d. ges. exper. Med. **96**:499, 1935.

26. Stern, L., and Gautier, R.: Recherches sur le liquide céphalo-rachidien, Arch. internat. de physiol. **17**:138, 1921; **17**:391, 1922; **20**:403, 1923.

27. Spatz, H.: Die Bedeutung der vitalen Färbung für die Lehre vom Stoffaustausch zwischen dem Zentralnervensystem und dem übrigen Körper, Arch. f. Psychiat. **101**:267, 1933.

spinal fluid, mediated by the choroid plexus, is independent of that of the blood and brain, mediated by the cerebral blood vessels. Although certain parallelisms exist between the two systems, they are quite distinct. The hematoencephalic barrier, as discussed in much of the literature, comprises two divisions, the blood-brain and the blood-cerebrospinal fluid barrier. Much of the credit for the separation of these two systems belongs to Walter.[28] For additional data on the relationship of the blood and the cerebrospinal fluid books by Kafka [29] and Katzenelbogen [30] are useful. In the present paper, I shall not be concerned with the blood-cerebrospinal fluid system but shall restrict myself to the blood-brain barrier (which is the etymologically correct rendition of the term "hematoencephalic").

Although several theories regarding the blood-brain barrier appear in the literature, only two are of significance today. The others are adequately criticized in Spatz's [27] excellent review. The two concepts which are of present day importance are: (*a*) The barrier between the blood and the brain resides in the capillary endothelium; and (*b*) the brain tissue has no affinity for the dye.

(*a*) *Concept of an Endothelial Barrier.*—The role of the endothelium in preventing passage of substances from the blood to the nervous system was first enunciated by Lewandowsky [1] and more recently amplified by Spatz.[27] The theory rests on one fundamental principle. A given substance, such as ferrocyanide or trypan blue, easily affects the nervous system when placed in the spinal fluid but does not pass into the brain when introduced into the blood stream. Spatz, working with trypan blue and repeating the experiments of Goldmann,[2] presented especially clear evidence on the subject. He injected massive doses of trypan blue intravenously into rabbits and after a few hours examined thick, unstained frozen sections of the brain. Although the brain grossly had a bluish tint, it could be seen under the microscope that the dye was entirely within the blood vessel. The color of the gross brain was due to intravascular dye. The brain tissue proper, between the blood vessels, was unstained. On the other hand, similar sections of liver showed that the dye was outside the blood vessels, in the parenchyma. Thus, in fresh preparations Spatz showed that trypan blue does not leave the blood vessels of the brain but does pass through the blood vessels of the liver.

28. Walter, F. K.: Die Blut-Liquorschranke, Leipzig, Georg Thieme, 1929; Die "Blut-Hirn-Schranke," Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:580, 1930; Die allgemeinen Grundlagen des Stoffaustausches zwischen dem Zentralnervensystem und dem übrigen Körper, Arch. f. Psychiat. **101**:195, 1933.

29. Kafka, V.: Die Zerebrospinalflüssigkeit, Leipzig, Franz Deuticke, 1930.

30. Katzenelbogen, Z.: The Cerebrospinal Fluid and Its Relation to the Blood: A Physiological and Clinical Study, Baltimore, Johns Hopkins Press, 1935.

With reference to the brain, one of two factors may be operative. Nerve tissue repels, that is, has no affinity for, the dye. This claim, according to Spatz, is controverted by the evidence of subarachnoid injection, by which the dye easily penetrates the nervous system when placed in direct contact with it. The other reason can only be that the vascular endothelium of the brain prevents passage, although endothelium elsewhere does not. In other words, the barrier resides in the endothelium.

(*b*) *Concept of Lack of Affinity.*—Rachmanow,[4] in 1913, first hazarded the mere suggestion that nerve tissue has no affinity for trypan blue, but this concept attracted no attention. In 1928, however, Mendel [31] revived the theory on the basis of the following experiments. After needle wounds were made in the brains of rabbits, trypan blue was administered intravenously. The area of injury stained vitally, and microscopic examination showed many ganglion cells containing the dye in granular or diffuse form. However, there were many other adjacent cells in the injured area which did not take up the trypan blue and which were morphologically normal. When sections of the injured area were studied with histologic stains (cresyl violet and carmine), there were noted differences in reaction between cells which were vitally stained and those which were not. These histochemical differences in staining were arbitrarily considered to be due to hydrogen ion concentration. The conclusion was reached that normally all cells of the nervous system are easily reached by trypan blue but that normal cells do not take up the dye because of a lack of affinity, which is correlated with the intracellular p_H. In an area of injury the p_H of some cells is altered; affinity develops, and the dye then enters the cell. Other cells in the injured region may retain their normal p_H and not take up the dye.

Schmid [19] confirmed the data of Mendel, using diathermy as the method of injury. Schmid expressed the belief that through the injury the adsorption relations of nerve tissue were altered; thus, he claimed, his observations supported Mendel.

Mendel's claim that normally the nerve cells are easily reached by the dye but that an intracellular factor prevents storage is clearly untenable. Spatz pointed out that the dye does not leave the blood vessels. Hence it cannot attain the immediate environment of the cell, where alone a lack of cellular affinity would be meaningful. In other words, the dye does not even come in contact with the cell. Furthermore, when trypan blue is placed directly in the cerebrospinal fluid the nerve cells stain with ease. This, to Spatz, proved that cellular affinity has no

31. Mendel, W.: Versuche über das Eindringen intravenös injizierten Trypanblaus in das künstlich verletzte Grosshirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:148, 1928.

bearing on the problem, but that only a vascular barrier can adequately explain the failure of normal nerve tissue to stain with trypan blue when given intravenously.

TISSUE AFFINITY FOR TRYPAN BLUE

Although Mendel's claim that the intracellular factor is the sole explanation has been adequately refuted by Spatz, the broader question of tissue affinity has not been touched. For this, a new set of data must be considered.

Practically all the published work on vital staining has been done with the use of chronically stained animals; that is, a number of doses of trypan blue are given at intervals of from one to two days; the animal is killed from twenty-four to forty-eight hours after the last injection, and the tissue is fixed and sectioned for microscopic examination. The rationale of this procedure is that the flocculation of dye by susceptible cells takes time and that injection of repeated small doses at intervals is the best method of saturating the susceptible cells. The trypan blue once aggregated into intracellular granules is resistant to the procedures of histologic technic and is brilliantly in evidence in properly prepared sections.

However, intracellular storage is really a secondary phenomenon. If a moderate dose of trypan blue is given intravenously the whole animal becomes blue within a few seconds. The dye is in the tissues, producing its characteristic coloration; yet there are no intracellular granules to be seen. There has been insufficient time for flocculation or colloidopexy. If the animal is killed at least twelve hours after the injection, a few granules will be visible in the usual histologic preparations; yet meanwhile the animal is deeply stained on observation with the naked eye. The problem remains: What is the cause of the blue color? Where is the dye before it becomes flocculated?

There are two methods of approach to this problem. Fresh tissue, removed a few minutes after an intravenous injection of dye, may be examined directly under the microscope in a clearing agent, such as glycerin; or blocks of tissue may be fixed, rapidly dehydrated, embedded, sectioned and examined unstained. In a series of experiments which are described *in extenso* elsewhere,[31a] I have employed both methods and have found them to yield results in essential agreement. A brief résumé of the results may be given here.

Mice and guinea pigs, which lend themselves easily to intravenous injection, were utilized. After intravenous administration of the dye,

31a. King, L. S.: Vital Staining of the Connective Tissues, J. Exper. Med. **68**:63. 1938.

fresh tissue was cleared directly in glycerin, while for permanent preparations Heidenhain's Susa fixative was employed. Fixation and dehydration were completed within a few hours. Paraffin sections of 30 microns were examined unstained.

Casual observation of the internal organs of a mouse or guinea pig ten minutes after an intravenous injection reveals that the skin, mucosae and internal organs are all stained. The color, however, varies from one organ to another. Microscopic examination of fresh or fixed tissue reveals that the blue color is due to diffuse staining of the connective tissue. Any of the hollow viscera shows this admirably. Epithelium is unstained, as is the smooth muscle, while the tunica propria is brilliantly outlined and the peritoneal surface and connective tissue muscle septums are slightly less so. Skeletal muscle affords equally striking preparations, with septums and fascial planes, or in the case of the diaphragm the pleural and peritoneal surfaces, sharply outlined in blue, while the muscle fibers are unstained. Sheets of connective tissue, such as the dura mater or the capsule of the kidney, are well colored. Dense connective tissue, such as tendon, is somewhat paler than the looser tissue.

In the parenchymatous organs, such as the kidney, the connective tissue is also outlined in blue. In good preparations the basement membrane of the tubules forms a sharp contrast to the tubular epithelium. In the spleen the capsule and trabeculae are vividly outlined. The pulp in fresh preparations is colorless, but in thin fixed sections some of the reticulin is also outlined faintly in blue. It must be emphasized that the resolving power of the microscope is less with a thick section cleared in glycerin than with a thinner fixed section more adequately cleared in xylene and mounted in balsam.

Reticulin stains with varying intensity. The argyrophilic framework of adipose tissue, for example, is brilliant. In the uterus, for example, it is much paler, while in the spleen, as already mentioned, it is not only pale but incomplete.

Petroff [32] and others have previously called attention to staining of the walls of the blood vessels at brief intervals after the administration of trypan blue. Petroff, who made no mention of the staining of connective tissue, concluded that the coloring of the blood vessels was due to staining of the elastic fibers. The elastic fibers all over the body, in fact, become deeply colored by trypan blue at a very brief interval after the dye is administered. But the diffuse staining of the connective tissue already mentioned is not due merely to the contained elastic fibers.

32. Petroff, J. R.: Ueber die Vitalfärbung der Gefässwandungen, Beitr. z. path. Anat. u. z. allg. Path. **71**:115, 1923. The literature on this subject has recently been reviewed by G. L. Duff (Vital Staining of the Rabbit's Aorta in the Study of Arteriosclerosis, Am. J. Path. **8**:219, 1932).

This is readily proved by elastic tissue stains of the organs in question. The trypan blue is held not merely by elastic fibers but also by collagen and reticulin.

The foregoing brief account applies to tissue examined a few minutes after the dye is injected. If examination is deferred for twenty-four hours the observations are somewhat different. Much of the dye has been excreted during this interval, and there has been ample time for the formation of intracellular granules. Preparations made after twenty-four hours show numerous granule-laden macrophages and also many granules within certain epithelial cells. In addition, however, there persists a faint, diffuse coloration of the connective tissue, similar to that occurring ten minutes after the injection but vastly reduced in intensity. With the lapse of forty-eight hours the diffuse color has practically disappeared from the sections, and only the intracellular granules remain.

It follows as a corollary that the intracellular storage of trypan blue in granular form depends on two factors: First, the dye must be present in the tissue in diffuse form, and, second, a given cell must have the intrinsic ability to flocculate the dye into granules. It has been seen that in the connective tissue the trypan blue appears diffusely almost immediately after injection. The dye is equally available to all contained or contiguous cells; yet it is stored in granular form only by certain cell types. Thus, histiocytes exhibit granules after small doses; fibroblasts, only after large, repeated doses. Various types of epithelial cells may or may not store the dye, depending on the concentration. On the other hand, such elements as glomerular epithelium or striated muscle will not show granules of trypan blue as long as they are healthy, regardless of the concentration. For a good description of what cell types will or will not aggregate trypan blue under normal conditions, the papers of Cappell [33] may be consulted. Such storage is clearly secondary to the diffuse presence of the dye.

The problem of affinity for trypan blue now becomes better defined. By the term "affinity" I mean the diffuse union of dye and tissue elements, antecedent to any colloidopexic or granular storage by discrete cells. Synonymous with "affinity" is "binding power." Connective tissue (that is, collagen, reticulin and elastic fibers) exhibits such affinity, holding the dye by a firm bond until it is excreted or segregated into granules by contained or contiguous cells. The strength of the bond varies from one element to another. In general, elastic fibers probably exhibit the firmest union with the dye. The bond of union between dye and tissue may be a phenomenon of adsorption, but in the absence of positive data the more noncommittal term "affinity" is adequate.

33. Cappell, D. F.: Intravitam and Supravital Staining, J. Path. & Bact. **32**:595, 1929.

The special accumulation of trypan blue in areas of inflammation is relevant to the concept of affinity. Menkin [34] has devoted considerable study to this problem and has brought forward the concept that the thrombosis of lymphatic vessels in an inflammatory focus determines the accumulation of dye.

In spite of the great mass of important evidence that Menkin has adduced, this explanation is not altogether adequate. In the central nervous system trypan blue will accumulate in an inflamed area in the same way as in the connective tissue. In the nervous system there are no lymphatics nor any substitute therefor. (The Virchow-Robin spaces cannot be regarded as substitutes for the lymphatics of the connective tissue.) Since the accumulation of trypan blue in areas of inflammation is a more general phenomenon than the plugging of lymphatics, the latter cannot be construed as the direct cause of the former.

Increased vascular permeability is of obvious and extreme importance in the mechanism of inflammation; yet this factor alone is not the complete explanation of increased storage of trypan blue. The dye is not merely carried passively into the tissue by the exudation of plasma. Thus, Macklin and Macklin [16] noted accumulation of trypan blue injected as late as thirty-five days after a simple injury to the brain. With this lapse of time after the initial injury, exudation is negligible; yet the dye was selectively drawn out of the blood vessels into the injured brain.

The key to the problem lies in the question of selectivity. For example, in certain types of inflammation there is increased permeability of the blood vessels to polymorphonuclear leukocytes, which appear in great numbers, while lymphocytes do not pass through the vessels until much later. Some factor apart from the wall of the vessel must account for this selectivity, and this factor must reside in the tissue itself. It is generally called by the noncommittal name chemotaxis. Recently, Menkin [35] isolated a crystalline substance which appears to play a role in the selective outpouring of the leukocytes; he called it "leukotaxine." The recent studies of Grand and Chambers [36] on the movement of leukocytes toward injured tissue in culture are also of great significance. In

34. Menkin, V.: Studies on Inflammation: I. Fixation of Vital Dyes in Inflamed Areas, J. Exper. Med. **50**:171, 1929; Inflammation: A Protective Mechanism, Arch. Int. Med. **48**:249 (Aug.) 1931; Studies on Inflammation: V. The Mechanism of Fixation by the Inflammatory Reaction, J. Exper. Med. **53**: 171, 1931; VIII. Inhibition of Fixation by Urea: A Further Study on the Mechanism of Fixation by the Inflammatory Reaction, ibid. **56**:157, 1932.

35. Menkin, V.: Studies on Inflammation: XIV. Isolation of the Factor Concerned with Increased Capillary Permeability in Injury, J. Exper. Med. **67**: 129, 1938; XV. Concerning the Mechanism of Cell Migration, ibid. **67**:145, 1938.

36. Grand, C. G., and Chambers, R.: Chemotactic Reactions of Leucocytes to Irritated Tissues, J. Cell. & Comp. Physiol. **9**:165, 1936.

the near future probably much more light will be cast on this problem. Meanwhile, one can say only that there appears to be some extravascular factor resident in the tissues which selectively calls forth the polymorphonuclear leukocytes in the inflammation.

I suggest that an analogous factor is responsible for the selective accumulation of trypan blue in an inflamed area. Elsewhere,[21b] I have expressed the hypothesis that the noxious agent in inflammation which alters the permeability of capillaries acts simultaneously on the tissue as a whole to alter its binding power for trypan blue. In this sense, the primary cause of the accumulation of dye in an inflammatory focus is an intrinsic change in the tissue, leading to heightened binding power. The actual alteration of the vascular wall may thus be of less importance than the change in the extravascular tissue. There is no question that a capillary in an inflamed area is more permeable than normal. The contention here made is not that the change in the capillary is the primary cause of the increased storage of dye but that the binding power of the tissue must be taken into account.

TRYPAN BLUE AND THE NERVOUS SYSTEM

The concept of affinity, therefore, implies binding of trypan blue diffusely in the intercellular matrix, where the dye is equally available to all cells and is in time aggregated into intracellular granules by cells which have a capacity for so doing. Although the discrete factors involved are not known, the behavior of connective tissue toward trypan blue may be described as indicating an affinity.

Let it be assumed that the central nervous system, with its unique constitution, has a lack of affinity; that is, the factors responsible for the behavior of connective tissue are absent in the brain. Now, the central nervous system alone, of all the organs of the body (the circulating blood excepted), possesses no true framework of connective tissue. Slight amounts of connective tissue accompany the blood vessels but do not constitute a true stroma. The nervous system has its unique glial stroma. If a section of any other organ of a vitally stained animal is examined, dye may or may not be found in the parenchyma, but an abundance will always be found in the stroma. In the central nervous system, unlike striated muscle, lung and testis, the dye cannot penetrate the connective tissue septums because they do not exist. According to my hypothesis, the dye cannot penetrate the nerve parenchyma because of a lack of affinity. Therefore, the dye does not penetrate at all, and the nervous system remains uncolored.

With this hypothesis, some of the facts presented in the first portion of this paper may be examined. Goldmann's original researches established the fact that the dura mater and the choroid plexus stain vitally.

The dura is pure connective tissue and is outside the scope of the present inquiry. The choroid plexus consists of a connective tissue stroma and the epithelial cells of the plexus. Within a few minutes after intravenous injection of trypan blue, this portion of the nervous system becomes diffusely colored, as does connective tissue elsewhere in the body. The dye in the stroma is available to the contained histiocytes and the adjacent epithelial cells. With the more usual manner of studying the vital staining reaction, that is, with numerous repeated doses, the histiocytes exhibit granules with small doses, whereas the epithelial cells require larger doses, again behaving like organs elsewhere in the body. Contrary to the contention of Spatz, there can be no question of a barrier between the blood vessels of the choroid plexus and the choroid plexus itself. With reference to the cerebrospinal fluid, the function of the barrier resides solely in the epithelium. The choroid plexus as a whole acts exactly like the adrenal gland or the intestine so far as its behavior toward trypan blue is concerned.

The vital staining of cells in the leptomeninges presents an interesting problem. These cells are in contact with the reticulin trabeculae of the pia-arachnoid, to which they are attached. On the other hand, they are bathed in the cerebrospinal fluid. The dye which they store can reach them in one of two ways: via the cerebrospinal fluid or via the connective tissue framework. Trypan blue may appear in the cerebrospinal fluid after intravenous administration, but overwhelming single doses (Spatz) or many repeated smaller doses (Baumann [37]) are necessary. Vitally stained cells in the leptomeninges are demonstrable with much smaller doses than those just described. It is conceivable that the dye enters the cerebrospinal fluid in minute amounts and is then flocculated by the histiocytes, but there is little evidence that this actually occurs. On the other hand, in favorable preparations it may be shown that shortly after intravenous administration of the dye the pia-arachnoid and the adventitia of the larger blood vessels contained therein are diffusely colored. The dye has already passed through the endothelium and is held in the connective tissue elements, from which it may be removed by the histiocytes. This color cannot be demonstrated in the finer meshes of the pia-arachnoid, but this may be due to the inadequacy of the methods of examination. The explanation that the dye readily passes the endothelium and is held by the connective tissue and reticulin until flocculated by the cells or excreted is at least consistent with the known facts and has experimental evidence in its favor.

The pineal gland, which stains vitally, is comparable to any other gland, such as the adrenal; that is, it consists of parenchymatous cells

37. Baumann, W.: Das Verhalten des Liquor cerebrospinalis bei experimenteller Anämie und vitaler Färbung, Deutsche med. Wchnschr. **46**:10, 1920.

with a connective tissue stroma. The pineal gland does not resemble the neural parts of the brain. Its intrinsic parenchymatous cells are totally different from neurons, and it has a true stroma of connective tissue, which the rest of the brain lacks. Clearly, since the structure of the pineal gland is different from that of nerve tissue, such as the cortex or the brain stem, one would a priori expect its reaction to trypan blue to be different. This, in fact, is the case. It behaves toward the dye as does any gland elsewhere and not as does any neuronal part of the brain.

Analogous to the pineal gland, the area postrema, the little portion of tissue at the caudal end of the fourth ventricle, has a unique histologic constitution. As I have shown in a previous communication,[38] its cells have no counterpart in any other portion of the nervous system, except, perhaps, in the posterior lobe of the pituitary. Moreover, its blood vessels possess much more extensive perivascular sheaths than do those in the rest of the nervous system. This area contains more connective tissue than the rest of the brain, although it does not have a true mesodermal stroma, as does, for example, the pineal gland. As compared with the rest of the nervous system, it has a different cell type and more connective tissue. It is non-neural. Consequently, one should not expect the lack of affinity of the rest of the nervous system to be applicable to this region.

The paraphysis and infundibulum have never been adequately studied histologically. Ordinary hematoxylin and eosin sections, however, suggest a similarity to the area postrema. In the absence of positive data, it can only be said that these structures also appear to be non-neural and to be closer to the area postrema than to other parts of the brain.

Both lobes of the pituitary gland stain vitally. The anterior lobe is not a derivative of the nervous system and is not a part of the present problem. The posterior lobe, the histologic structure of which has been best studied by Bucy,[39] is in many ways comparable to the area postrema. The cell type is unique; there is vastly more connective tissue in relation to the blood vessels than in the rest of the brain, and, although this gland is unlike the area postrema in receiving large bundles of nerve fibers, it is non-neural in nature and function. In a manner, it, like the area postrema, is in the nervous system but not of it.

The peripheral nerves, the spinal ganglia and the sympathetic and parasympathetic ganglia all stain vitally with much greater ease than does the central nervous system. These structures contain much the same elements as are observed in the central nervous system—neurons, myelinated and unmyelinated fibers, capsular cells and Schwann cells, which

38. King, L. S.: Cellular Morphology in the Area Postrema, J. Comp. Neurol. **66**:1, 1937.

39. Bucy, P. C.: The Pars Nervosa of the Bovine Hypophysis, J. Comp. Neurol. **50**:505, 1930.

have been compared to oligodendroglia cells. Yet all these peripheral types of structures differ in one important respect from the central nervous system: In the peripheral organs there is an extensive connective tissue framework. Since connective tissue has an affinity for trypan blue, one would expect these peripheral segments of the nervous system to stain vitally.

It has already been mentioned that with long-continued administration of trypan blue many cells within the parenchyma will stain vitally, especially around the central canal and within the cornu ammonis. In terms of the theory stated, this would be explained by the assumption that the lack of affinity of the nervous system for the dye is not absolute. With sufficient concentration small amounts permeate the nerve tissue, to be flocculated by suitable cells. Such minute amounts of dye are not visible in acute experiments, but it is necessary to assume that the dye is present in the tissue in subvisible concentration.

The brains of neonatal animals are vitally stained much more easily than those of adults. This difference in behavior between the very young and the adult cannot, obviously, be explained by the connective tissue factor. However, the constitution of very young nerve tissue is different from that of the adult brain. Apart from differences in cellular morphologic pattern and distribution, the young brain has vastly less myelin and a much higher water content.[40] It is reasonable to assume that these differences in anatomic and chemical structure may be correlated with the greater affinity for trypan blue. It is, furthermore, of interest that the brain is not the only organ the behavior of which toward trypan blue is different in the neonatal state than in the adult. Blotevogel [41] demonstrated such differences for the teeth and the eye. The receptivity of the neonatal brain to trypan blue does not represent a unique phenomenon, but is an example of the more general behavior of immature tissue.

In the explanation of vital staining of inflamed areas, the role of the concept of affinity has already been discussed. Evidence was presented in favor of the concept of increased binding power of inflamed tissue as compared with that of normal tissue. It was pointed out by Macklin and Macklin [16] that in a condition of inflammation the brain stains much less intensely than does injured bone. It is a common observation, moreover, that injured brain stains less than similarly injured connective tissue. From these facts, one may conclude that even in a state of inflammation the nerve tissue has less affinity for

40. Donaldson, H. H., and Hatai, S.: On the Weight of the Parts of the Brain and on the Percentage of Water in Them According to Brain Weight and to Age in Albino and in Wild Norway Rats, J. Comp. Neurol. **53**:263, 1931.

41. Blotevogel, W.: Der vitale Farbstofftransport während der Zahnentwicklung, Ztschr. f. Zellen- u. Gewebelehre **1**:607, 1924; Der vitale Farbstofftransport im jugendlichen Auge, ibid. **1**:447, 1924.

trypan blue than other organs in a similar condition. This slight affinity is intrinsic to the nervous system.

FACTS AND ASSUMPTIONS

The concept of affinity as previously discussed, is based on certain facts, together with certain unproved assumptions. In the case of administration of trypan blue by way of the blood stream the principal facts and corollaries are: 1. The central nervous system as a whole is practically unstained. 2. The connective tissue all over the body stains readily. 3. Connective tissue stroma is present in all organs, and is in contact with the great majority of cells, except in the central nervous system. 4. Certain areas of the brain which normally stain vitally (pachymeninges and leptomeninges, choroid plexuses and pineal gland) are composed largely of connective tissue and are thus similar to other non-nervous organs. 5. Certain other regions which also stain vitally, such as the area postrema and the posterior lobe of the pituitary, have more connective tissue than other parts of the brain, and the histologic structure is also widely different. 6. The peripheral nervous system, which stains vitally much more readily than the central nervous system, differs from the latter chiefly in the presence of an extensive connective tissue stroma and is therefore comparable to other non-nervous organs. 7. In the neonatal animal, which stains vitally more readily than the adult, the histochemical structure of the nervous system is different from that of the adult. 8. Inflamed or necrotic tissue of whatever kind has a stronger binding power for trypan blue than similar normal tissue.

The fact that some cells have an intrinsic capacity for flocculating trypan blue into intracellular granules while other cells do not is an interesting, but not an essential, observation. The important factor in the theory of vital staining is the diffuse presence or availability of the dye antecedent to cellular action.

The unproved assumptions are: 1. Connective tissue stains easily because of intrinsic factors the nature of which is unknown but which I designate by the general term "affinity." 2. These ultimate intrinsic factors are absent from true nerve tissue, a hypothesis which is summed up in the phrase: "The nervous system has no affinity for trypan blue." 3. Differences in tissue constitution (e. g., of the neonatal brain or the area postrema, as compared with that of the bulk of the nervous system) are indicative of differences in affinity for trypan blue. 4. The increased binding power of inflamed or necrotic tissue is due to a change in the intrinsic factors of the tissue, i. e., an altered affinity. (A fifth assumption is implied—that the paraphysis and infundibulum, which also stain vitally, are similar to the area postrema. There are no available data bearing on this point.)

The concept of affinity, like any other, cannot be demonstrated to be true or false. The most that can be asked of any hypothesis is that it cover the facts in an adequate fashion, that it should not be inconsistent with any known data and that it should not involve unnecessary or unreasonable assumptions. It is my belief that the hypothesis so far enunciated satisfies these criteria.

ENDOTHELIUM AS A "BARRIER"

An alternate hypothesis has been offered by Spatz [27] and, in less detail, by Friedemann.[42] After an extensive summary of the relevant literature, Spatz came to the following conclusion, among others: "Between the blood and the brain tissue there must be interposed a barrier which is not passable by trypan blue." [43] Further, the locus of "the barrier between the blood and the brain lies in the endothelium of the intracerebral vessels." [44]

Spatz devoted his efforts to showing that with intravenous administration the trypan blue does not leave the blood vessels and that therefore it is the endothelium which holds it back. In other words, the barrier is the endothelial membrane. He implied that if the endothelium were a little different the brain would stain readily. In line with this theory, he claimed that the vascular endothelium is intrinsically more permeable in the choroid plexus, leptomeninges, area postrema, infundibulum, tissues of neonatal animals, peripheral nervous system and so on. These structures are examples, in Spatz's terminology, merely of loci minoris resistentiae.

The concept of a membrane serving as a barrier deserves examination. Of course, a barrier may exist in a crudely mechanical sense. A collodion membrane the pores of which are too small will not allow the passage, e. g., of a virus particle that is greater than a given size. By the use of membranes of graduated pore diameter the size of many virus particles has been accurately determined. A membrane the pores of which are too small is an effective barrier. It is known, however, that vascular endothelium is not a barrier in this sense. Extensive experiments with dyes have shown that the charge of a dye particle, rather than its size, is the determining factor regulating passage into the brain.

It is a truism that in any system involving a semipermeable membrane the character of the medium on either side of the membrane is of

---

42. Friedemann, U.: Further Investigations on the Blood-Brain Barrier, J. Immunol. **32**:97, 1937.

43. *"Es muss also zwischen Blut und Gehirngewebe eine Schranke zwischengeschaltet sein, die für das Trypanblau nicht durchgängig ist."*

44. *"Die Schranke zwischen Blut und Gehirn ist in der Innenhaut der intracerebralen Gefässe . . . zu suchen."*

importance. A change in the nature of the solution on one side may influence the passage of ions through the membrane. For example, the laws of the Donnan equilibrium govern the changes in ionic distribution when a nondiffusible protein is added to one of two solutions in equilibrium, separated by a semipermeable membrane. The membrane remains the same, but there is a redistribution of ions in accordance with recognized laws. It would clearly be a faulty use of terms to say that the membrane suddenly became more or less permeable, because, for example, blood serum was added to one side. A second example was furnished by Friedemann. The dye alizarin blue S, dissolved in water or saline, readily passes across a semipermeable membrane until equilibrium is reached. If dissolved in serum, however, it will not pass through the same membrane. Obviously, the membrane did not suddenly become impermeable to the dye. Rather, the dye was bound to become nondiffusible.

In experiments in vitro it is relatively easy to determine the role played by the two mediums in regulating passage or nonpassage of a given substance across a membrane. But with experiments with trypan blue in vivo the task is not so simple. In comparing the brain with other organs, such as skeletal muscle, one finds that in the first case the dye does not leave the blood vessels (except in special areas, like the area postrema), while in the second case it does. The blood, laden with trypan blue, is clearly a constant factor in both instances. The vascular endothelium may or may not be similar. But the third factor in the two systems, the extravascular tissue, is certainly different in the two cases.

With respect to trypan blue, the concept of affinity maintains that the difference in behavior between, for instance, the cortex and the dura is due to the intrinsic differences between nerve tissue and connective tissue. The capillary endothelium may, in fact, be different in the two tissues, although, to my knowledge, there is as yet no direct evidence bearing on this point. Spatz, however, assumed such a difference, on the basis of indirect and, to my mind, inadequate evidence.

To be sure, Spatz admitted that the charge of a dye particle, as well as the character of the medium on either side of a membrane, is important in regulating passage across the membrane. In spite of this, however, he maintained that the barrier between the blood and the brain resides in the endothelium. He did so for one reason only, namely, that with subarachnoid injection of trypan blue the brain stains freely. In his opinion, this disposes effectively of the concept of tissue affinity, to which I have adhered so far.

The data on subarachnoid injection must be examined critically. Goldmann was the first to introduce trypan blue intrathecally into an animal, and subsequent investigators have added little new. When the dye is placed in the cistern, it has a characteristic distribution, chiefly

around the base of the brain, the cerebellum and the spinal cord. The convexity of the hemispheres is little stained. Curiously, the dye assumes the same distribution if injected into a cadaver.

The depth of penetration of the dye into the nervous system depends on the length of the experiment. This depth may be from a fraction of a millimeter to several millimeters. Spatz emphasized that the staining from the surface inward is diffuse and quite independent of tissue structure. The brain tissue, he said, behaves like a unitary colloidal mass, and there is no evidence that the dye passes along preformed pathways or respects differences in tissue constitution.[45]

The formation of discrete intracellular granules in various cells again depends on the length of the experiment. In twenty-four hours, in spite of good macroscopic color, few granules are visible in microscopic sections. Such granules are best seen in chronic experiments of several weeks' duration, with several intrathecal injections of dye. The length of the experiment does not alter the essential character. Intracellular aggregation of dye is a secondary phenomenon, and Spatz rightly emphasized that the gross macroscopic observations are of more significance than the microscopic.

Further interesting facts have been brought out by Spatz [27] and his pupils and by Jorns.[46] It is known that acid and basic dyes, as classes, behave quite differently when placed in the blood stream, not only toward the brain but toward other tissues. When placed in the spinal fluid, however, they behave essentially the same. Basic as well as acid dyes pass diffusely into the brain from the surface, with the depth of penetration roughly parallel to the diffusibility in gelatin.

There is a striking similarity between the action of dyes injected intrathecally in vivo and that of the same dyes acting in vitro. In the latter instance, if slabs of brain tissue are immersed in various solutions of dye, there is, as in the case of subarachnoid injection, diffusion inward from the surface, the depth of penetration being roughly determined by the degree of dispersion of the dye and the length of the experiment. Nor is the action in vitro restricted to nerve tissue. A

45. It thas been amply demonstrated (Woollard, H. H.: Vital Staining of the Leptomeninges, J. Anat. **58**:89, 1924. Kubie, L. S., and Schultz, G. M.: Vital and Supravital Studies of the Cells of the Cerebrospinal Fluid and of the Meninges in Cats, Bull. Johns Hopkins Hosp. **37**:91, 1925) that isolated dye granules are visible in the depths of the brain far removed from the areas of macroscopic coloration. This fact, however, does not establish the thesis that the dye wanders down the perivascular spaces as the ordinary mode of distribution. The diffuse penetration from the surface is clearly the general mode of entrance to the nervous system.

46. Jorns, G.: Experimentelle Untersuchungen über die Resorptionsvorgänge in den Hirnkammern, Arch. f. klin. Chir. **171**:326, 1932.

block of any organ, placed in the dye, will show the same penetration inward from the surface. Differences in the nature of the organs, the histologic structure and the charge of the dye exert no significant influence.

When the dye is injected intravenously, the endothelium is a semipermeable membrane. The passage of injected substances across it is determined partly by the nature of the membrane and partly by what is on either side of the membrane. The two mediums, together with the endothelium, form a complex system. The system will be quite different when the membrane is not involved, as in the case of subarachnoid injection or of immersion of brain tissue in vitro in dye solutions.

Recently, Friedemann [42] has performed extensive comparative experiments, placing brain tissue in solutions of various dyes dissolved in serum and determining the minimum concentrations necessary for staining the tissue. His results are of interest, but his attempt to correlate them with the action of the same dyes injected intravenously is of questionable validity. The conditions of the two sets of experiments are utterly dissimilar. It is impossible to neglect the influence exerted by a membrane such as the vascular endothelium, which is present in the one case and absent in the other.

Indisputably, the presence of the vascular endothelium is of extreme importance in explaining the divergent results of intravenous and intrathecal injection of trypan blue. It does not follow, however, that the endothelium of the brain is therefore different from the endothelium elsewhere in the body. The theory of affinity postulates that unknown intrinsic factors in the extravascular tissue determine, by their presence or absence, the passage of trypan blue from the blood stream across the endothelium into that tissue. Connective tissue is considered to have a high, and nerve tissue a corresponding low, affinity. These intrinsic factors are related to the tissue constitution and are operable only in relation to the blood stream and the vascular endothelium. With trypan blue placed in the cerebrospinal fluid an entirely different system is involved, and these hypothetic factors, no longer in their proper relation, are irrelevant.

This point may be illustrated by analogy. If trypan blue is injected intravenously and the spleen is examined after a few minutes, it is found that the capsule and trabeculae are vivid blue while the pulp is not stained. On the other hand, immersing in vitro a block of spleen in a solution of trypan blue results in a homogeneous blue zone of diffusion, wherein trabeculae and pulp are stained uniformly. Clearly, the intrinsic differences between the capsule or trabeculae and the pulp, which are selective factors and determine the staining in vivo, are not operative with immersion in vitro. While still existing in fact, these intrinsic differences are irrelevant to the conditions of the latter experiment.

With any organ whatever, immersion in vitro in trypan blue gives results which are altogether different from true vital staining by way of the blood stream. The brain is no exception. Injection of the dye into the subarachnoid space approximates immersion of the tissue in vitro. Such an experiment does not tell one anything, directly or indirectly, about the nature of the vascular endothelium. It throws no light on the laws governing passage across a membrane. It has no bearing on the problem of affinity, a problem which has meaning only in relation to the endothelium.[47]

It is not maintained that all endothelium of all organs is exactly alike. The endothelium of the brain may, indeed, be different from that of any other organ, but there is as yet, to my knowledge, no direct evidence that this is the case. Such a difference would be purely hypothetic. As an *ad hoc* hypothesis to explain the facts of vital staining it is utterly lacking in cogency.

Much of the literature on the hematoencephalic barrier has been concerned with the locus of the barrier. The prevailing opinion heretofore has been that "the" locus is the endothelium, with the implication that if the endothelium were just a little different the brain would stain with ease. According to the concepts which have been developed here, it is false to consider the barrier as having a unitary locus. The barrier, if one is to continue to use the term, lies in the relationship between the blood and the brain across the endothelium, thus forming a system which is different from that in any other organ. It is here maintained that the principal reason for this difference lies in the unique constitution of nerve tissue.

SUMMARY

With the intravenous injection of trypan blue and many other negatively charged substances the brain as a whole, except for certain regions, remains uncolored, although other organs stain readily. Two possible explanations are at hand: that the vascular endothelium of the brain differs from that in other organs or that the brain has no affinity for trypan blue. Against the latter conception is the fact that the dye

47. There are several facts in relation to intrathecal injection of trypan blue that deserve mention. It was first pointed out by Woollard that when this dye is placed in the cerebrospinal fluid the choroid plexuses do not stain. They appear grossly colorless, in contrast to the deep blue of the adjacent tissue. This fact has been repeatedly confirmed. M. Mandelstamm and L. Krylow (Vergleichende Untersuchungen über die Farbenspeicherung im Zentralnervensystem bei Injektionen der Farbe ins Blut und in den Liquor cerebrospinalis, Ztschr. f. d. ges. exper. Med. **60**:63, 1928) claimed, in addition, that the area postrema and other special regions which take up the dye from the blood stream do not stain when the dye is injected into the cerebrospinal fluid. These data are difficult to interpret.

placed in immediate contact with nerve tissue, as in the case of subarachnoid injection, stains the nerve tissue readily.

The concept of affinity is defined to mean the presence in the tissue of certain unknown factors by which the dye carried in the blood is bound diffusely and rendered available to all contained or contiguous elements. In this sense the connective tissue all over the body is demonstrated to have a high affinity for trypan blue. Attention is called to the fact that the brain is unique among the organs of the body in not having a connective tissue stroma (i. e., intercellular septums of connective tissue, apart from the walls of the blood vessels). All other organs may have cells which do not normally stain with trypan blue; yet these cells are in relation to connective tissue septums. In the brain such intercellular septums do not exist.

It is postulated that whatever factors in connective tissue are responsible for the drawing of trypan blue from the blood stream and holding it in a loose bond are not present in the nerve tissue proper, so that nerve parenchyma, unlike connective tissue, has a lack of affinity for trypan blue. These factors determining affinity are to be correlated with the constitution of the tissue. It is then shown that all the special regions of the brain which stain vitally are characterized by an extensive connective tissue stroma (whereby they resemble other nonneural organs in the body) or a tissue constitution totally different from that of the rest of the brain or both.

The fact that passage across a semipermeable membrane is largely determined by the medium on either side of the membrane is reviewed, and the importance of the electrical charge of an injected dyestuff is emphasized. The unique constitution of nerve tissue is held to be the determining factor regulating the passage of basic dyes and the nonpassage of acid dyes into the brain.

The theory of a vascular barrier, in which the vascular endothelium of the brain is considered to be in some sense different from that elsewhere in the body, is discussed. The force of this argument rests on (*a*) the established fact that dyes injected intrathecally penetrate the brain tissue and (*b*) the assumption that this fact demolishes the theory of affinity. It is pointed out that the conditions of subarachnoid and of intravenous injection are so dissimilar that this assumption is untenable. The facts of subarachnoid injection have no bearing on the theory of affinity and consequently do not invalidate it.

It is not maintained that all endothelium is identical throughout the body. It is merely pointed out that the postulate of a hypothetic peculiarity of the endothelium of the brain to explain the facts of vital staining is purely an *ad hoc* argument, lacking in cogency. The facts which this postulate is designed to explain can be better interpreted by the concept of affinity.

EPILEPTOGENIC CORTICAL SCARS

RESULTS OF SURGICAL REMOVAL

WILLIAM J. GERMAN, M.D.
NEW HAVEN, CONN.

The surgical treatment of traumatic epilepsy is chiefly a product of the postwar period. Interest in this subject received its primary impetus from the works of Foerster,[1] in Europe, and of Penfield and his associates,[2] in America. At present, widespread attention is being directed toward many phases of the problem of convulsions. It appears desirable, therefore, to analyze the surgical results obtained by various workers in this rather specialized field.

It is of paramount importance that any form of therapy, especially one of such magnitude as surgical removal of the cerebral focus, should be based on fundamental knowledge of the disease process. Though many gaps exist in the present understanding of the convulsive mechanism, the basic factor of a primary cerebral focus seems fairly well established in a certain group of cases. Thus, a tumor, cicatrix, degenerative area or porencephalic lesion may set off the complex sequence of physical and chemical events which is termed a convulsion. However, this is not an inevitable result of such a lesion; in fact, the relative infrequency of epilepsy after major cerebral trauma suggests that most cortical lacerations are not productive of convulsions. Regardless of this determining factor, surgical efforts at present are directed toward removal of the irritative focus. This requires accurate preoperative localization of the lesion.

From the Department of Surgery, the Yale University School of Medicine.

Read before the Section on Nervous and Mental Diseases at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 17, 1938.

1. Foerster, O.: Zur operativen Behandlung der Epilepsie, Deutsche Ztschr. f. Nervenh. **89**:137, 1925; Die Pathogenese des epileptischen Krampfanfalles, ibid. **94**:15, 1926. Foerster, O., and Penfield, W.: Der Narbenzung am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung für das Zustandekommen der Anfälle, und für therapeutische Bekämpfung derselben, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:475, 1930.

2. Penfield, W.: Radical Treatment of Traumatic Epilepsy and Its Rationale, Canad. M. A. J. **23**:189, 1930; Evidence for a Cerebral Vascular Mechanism in Epilepsy, Ann. Int. Med. **7**:303, 1933; Epilepsy and Surgical Therapy, Arch. Neurol. & Psychiat. **36**:449 (Sept.) 1936. Penfield, W., and Gage, L.: Cerebral Localization of Epileptic Manifestations, ibid. **30**:709 (Oct.) 1933.

A localizing diagnosis is dependent on many factors, any one of which may supply the desired clue. The history of injury at birth or later, a focal characteristic of the convulsions, neurologic signs of a localizing nature and presence of a depressed fracture are of extreme importance and may be determined by careful taking of the history, examination and roentgenographic studies. The observation of a convulsion, either spontaneous or induced, with neurologic findings during the immediate postconvulsive period, may contribute significant information. Pneumoencephalographic examination is a valuable but not an infallible diagnostic aid. The electroencephalographic procedure promises further extension of the focal diagnosis.

The gross localization of the lesion having been established, more exact cortical definition often becomes necessary when the suspected cerebral locus is exposed. Although cortical scars are usually visible on the surface, confirmation of the convulsive sequence by electrical

TABLE 1.—*Results of Surgical Treatment in 29 Cases of Epilepsy Classified According to the Type of Lesion*

Results	Scar	Porencephaly	Degeneration	Total Cases
Freedom from major attacks	7	2	3	12
Rare major attacks	4	..	3	7
Frequent major attacks	4	2	3	9
Fatal outcome	1	..	..	1
Total number of cases	16	4	9	29

stimulation forms the final step in the diagnostic process. Even more important is localization of subcortical scars and degenerations by electrical stimulation. In order to maintain an active level of cortical irritability, especially when localization may depend on electrical reproduction of sensory phenomena, the operations are performed with the use of local anesthesia. It appears likely that determinations of cortical action potentials and possibly of hydrogen ion concentrations may soon play a part in the procedure of cortical exploration for the explosive focus. The involved area having been defined, it is completely removed, with a minimum of trauma and hemorrhage. Finally, all patients are instructed to continue medication with phenobarbital for a considerable period after operation.

The present report is based on the results in 29 cases, after intervals of from one to eight and a half years following cerebral surgical procedures for the treatment of epilepsy. The cases have been divided into three pathologic groups on the basis of the presence of (1) scars, (2) porencephaly or (3) degenerations. The results are shown in table 1.

RESULTS

There was 1 death in the series, a mortality of about 3.5 per cent.

In 19 of the 29 cases there was complete or partial relief from convulsive symptoms. Frequent major attacks continued in 9 cases. The standard operative procedure of complete excision was followed in 14 of the 16 cases in which there were cortical scars. The results in this group were satisfactory in 11 patients, 4 being completely relieved from convulsions (cases 1, 9, 12 and 14) and 6 definitely improved (cases 3, 4, 8, 11, 15 and 16). Frequent major attacks continued in 3 cases (cases 5, 6 and 10), and 1 patient died (case 7). Of the 2 remaining cases, lysis of meningeal adhesions was successful in 1 (case 13) and failed in the other (case 2). Of the group of cases of porencephaly, simple uncapping and lysis of adhesions were successful in 2 (cases 19 and 20) and failed in 2 (cases 17 and 18). In the last 2 cases a second operation was recently performed, with excision of the cicatricial porencephalic wall. The operative procedures were somewhat more varied in the cases in which there was cortical degeneration. Complete excision was carried out in 3 cases (cases 26, 28 and 29), with success in 2 (cases 28 and 29). Incomplete excision was carried out in 4 cases, with success in 1 (case 23) and improvement in 3 (cases 21, 22 and 24). Lysis of meningeal adhesions gave only temporary relief (for one year) in 1 instance (case 27), and excision of motor areas (for the face and arm) failed to control convulsions in 1 (case 25). In spite of the lack of standardization of surgical procedures in the cases of degenerative lesions, favorable results were obtained in 6 of the 9 cases.

An analytic comparison of the successes and failures in this series of cases has been attempted on the basis of clinical, pathologic and therapeutic characteristics. The term "cure" has been purposely avoided because of its implication of finality. In its place, "success" has been used to denote freedom from convulsive episodes, while "improvement" indicates a marked decrease in frequency and severity of attacks. These two favorable classes have sometimes been combined under the term "satisfactory."

It is evident from the results just presented that the type of surgical procedure, though important, is not the only determining factor in prognosis. In the combined series, a second operation, with complete excision was performed in 2 cases, because of failure following partial extirpation. The radical procedure was successful in 1 case (case 28), that of a degenerative lesion, and failed in the other (case 6), that of a cortical scar. The type of pathologic lesion, though probably not without significance, was of only slight aid in establishing a prognosis. The results were somewhat better in the series of cases of cortical scar than in the other two groups.

The following clinical characteristics were considered: age of the patient; type, duration and frequency of convulsions; anatomic location of the lesion, and presumptive etiologic factors. From a prognostic standpoint, the age of the patient failed to show any significant correlation. However, comparison of the cases of scar with those of degenerations revealed an age span of from 5½ to 50 years, with an average age of 24.8 years, in the former group and of from 2 to 12 years, with an average of 6.4 years, in the latter.

The convulsions in 25 of the 29 cases had localizing characteristics. In the remaining 4 cases (cases 2, 11, 16 and 20) there were only generalized convulsions. The results in these 4 cases—satisfactory outcome in 1 (case 20), improvement in 2 (cases 11 and 16) and failure in 1 (case 2)—appeared to have no statistical significance. Convulsions were usually associated with loss of consciousness in 24 cases. Of the

TABLE 2.—*Correlation of Duration of Convulsions and Results of Surgical Treatment Expressed in Years*

Result	Less Than 1 Year	1 to 2 Years	2 to 3 Years	3 to 5 Years	5 to 10 Years	More Than 10 Years	Total Cases
Scars							
Success	1	3	..	..	1	..	5
Improvement	3	..	..	2	..	1	6
Failure	..	..	1	1	1	1	4
Total number of cases	4	3	1	3	2	2	15
Degenerations							
Success	1	..	1	1	..	..	3
Improvement	..	1	1	..	1	..	3
Failure	..	1	..	1	1	..	3
Total number of cases	1	2	2	2	2	..	9

remaining 5 cases, consciousness was retained in 3 and was lost only occasionally in 2. The results were: success in 2 instances (cases 14 and 19), improvement in 1 (case 15) and failure in 2 (cases 6 and 27).

In striking contrast to the lack of significant observations thus far reported, the temporal span during which convulsive episodes had been present showed a definite prognostic correlation (table 2). In 7 of the 11 cases of cortical scar in which results were satisfactory the duration of convulsions was not more than two years, while in all the 4 cases of failure there were convulsions for more than two years. In 4 of the 6 cases of degeneration in which the results were satisfactory convulsions had been present for three years or less, while in 2 of the 3 cases of failure convulsions had occurred for more than three years. The group of cases of porencephaly was too small to justify statistical analysis.

The maximum frequency of convulsions appeared to have no significant relation to prognosis. Approximately the same proportion of

satisfactory results was obtained with patients having many convulsions daily as with those in whom the frequency of convulsions was not greater than one per month. From a diagnostic point of view, it is noteworthy that patients with cortical degenerations exhibited a greater frequency of convulsions than those with cortical scars.

Analysis of the anatomic location of the lesion gave little evidence of prognostic significance. The parietal region was found to be the most frequent single site of all types of lesions, and the greatest proportion of satisfactory results was obtained in the group of parietal lesions.

The probable etiologic factor was determined in 25 of the 29 cases. A definite traumatic basis was present in 13 cases, while injury at birth was apparently responsible in 7 cases. Previous cerebral operation was the presumptive factor in 1 case, and thrombosis, in another. In 2 cases porencephaly was probably related to prenatal factors, and in 1 case it was perhaps secondary to infection. No relation could be established between etiologic factors and prognosis.

The results of pneumoencephalographic examination were of considerable diagnostic interest. The procedure was carried out in 22 cases, with significant findings in 13. The method failed to establish the diagnosis in 9 cases, in 5 of which there were cortical scars and in the remaining 4 degenerations. A depressed fracture of the skull was present in 2 cases; in fact, this contributed the only evidence of localization in 1 case of cortical scar (case 16).

The importance of electrical stimulation of the cortex was particularly striking in the group of degenerations in which accurate localization of the lesion was frequently accomplished only in this manner. Occasionally, in this group, a locus of cortical pallor or softening served to identify the area involved. In 2 cases of cortical scar (cases 14 and 15) the lesion was located only by the results of electrical exploration of the cortex.

Histologic study of the excised specimens yielded information on the probable pathologic sequence of events in formation of the various lesions. In the group of cases of cortical degeneration, various stages of destruction of ganglion cells were observed, ranging from mild swelling and nuclear changes, with occasional loss of ganglion cells, to complete disruption of the normal architectural pattern. In cases of the latter stage glial proliferation was noted, suggesting similarity to the true glial scars. The cortical scars were of two types: fibrous and glial. However, many of the fibrous scars were accompanied by considerable glial proliferation. Most of the fibrous scars contained old blood pigment, indicating their traumatic origin. In only 2 cases in the series (cases 11 and 15) were pure glial scars seen, and in these the astrocytic elements predominated. Glial scars were likewise observed in

TABLE 3.—*Data in 29 Cases of Epilepsy in Which Surgical Treatment Was Carried Out*

Case Number	Year of Operation	Result: Success	Result: Improvement	Result: Failure	Age at Operation, Years	Convulsions: Type: Localized	Convulsions: Type: Generalized	Convulsions: Type: Unconsciousness	Convulsions: Duration	Convulsions: Maximum Frequency: Monthly	Convulsions: Maximum Frequency: Weekly	Convulsions: Maximum Frequency: Daily	Convulsions: Maximum Frequency: Several Daily	Location of Lesion: Frontal	Location of Lesion: Central	Location of Lesion: Temporal	Location of Lesion: Parietal	Location of Lesion: Occipital	Operation	Etiologic Factor	Pneumo-encephalographic Findings
												Scars									
1	1930	x	..	..	8	x	x	x	2 mo.	..	..	..	x	..	..	..	x	..	Excision	Birth injury	+
2	1930	..	..	x	17	..	x	x	7 yr.	..	..	x	..	..	x	x	..	..	Removal of biopsy specimen	Trauma	+
3	1930	..	x	..	32	x	..	x	5 yr.	..	..	..	x	..	x	..	..	..	Excision	?	—
4	1931	..	x	..	19	x	x	x	1 mo.	..	..	..	x	..	x	..	..	..	Excision	Trauma	—
5	1931	..	..	x	5½	x	x	x	4 yr.	..	..	..	x	..	..	x	x	..	Excision	Birth injury	..
6	1931	..	..	x	31	x	..	..	3 yr.	x	..	..	..	..	x	..	..	..	Excision	Trauma	..
7	1932		Death		33	x	..	x	20 yr.	x	..	..	..	x	..	..	..	..	Excision	Trauma	+
8	1933	..	x	..	19	x	..	x	16 yr.	..	x	..	..	..	..	..	x	..	Excision	Trauma	..
9	1933	x	..	..	20	x	x	x	2 yr.	x	..	..	..	..	x	..	..	..	Excision	Trauma	+
10	1934	..	..	x	45	x	x	x	13 yr.	x	..	..	..	..	..	..	x	..	Excision	Trauma	+
11	1935	..	x	..	12	..	x	x	4 mo.	x	..	..	..	..	..	..	..	x	Lobectomy	Trauma	+
12	1935	x	..	..	50	x	x	x	2 yr.	..	..	..	x	x	..	..	..	..	Excision	Trauma	+
13	1935	x	..	..	39	x	..	x	2 yr.	..	x	..	..	..	..	x	..	..	Lysis	Operation	+
14	1936	x	..	..	21	x	x	x	8 yr.	..	..	..	x	..	x	..	..	..	Excision	?	—
15	1936	..	x	..	17	x	..	..	4 yr.	x	..	..	..	..	..	..	x	x	Excision	Trauma	—
16	1936	..	x	..	29	..	x	x	8 mo.	..	..	..	x	x	..	..	..	..	Excision	Trauma	—
												Porencephaly									
17	1929	..	..	x	17	x	x	x	8 yr.	x	..	..	..	..	..	..	x	..	Uncapping	Congenital	+
18	1934	..	..	x	12	x	x	x	15 mo.	..	..	..	x	..	..	..	x	x	Uncapping	Congenital ?	..
19	1934	x	..	..	36	x	..	..	5 yr.	x	..	..	..	..	..	..	x	x	Uncapping	Infection ?	..
20	1937	x	..	..	31	..	x	x	18 yr.	..	..	..	x	..	..	x	x	x	Uncapping	Birth injury	+
												Degenerations									
21	1929	..	x	..	2	x	x	x	18 mo.	..	..	..	x	..	..	..	x	..	Removal of biopsy specimen	?	..
22	1929	..	x	..	3½	x	x	x	3 yr.	..	..	..	x	..	..	..	x	..	Removal of biopsy specimen	Birth injury	—
23	1930	x	..	..	4	x	x	x	9 mo.	..	..	..	x	..	..	..	x	..	Removal of biopsy specimen	Birth injury; infection ?	—
24	1931	..	x	..	12	x	x	x	6 yr.	..	..	..	x	..	..	x	..	..	Removal of biopsy specimen	Thrombosis	—
25	1932	..	..	x	12 (Died 28 mo. later)	x	x	x	7 yr.	..	..	..	x	..	x	..	..	..	Excision of face and arm areas	Birth injury ?	—
26	1932	..	..	x	3½	x	x	x	18 mo.	..	..	..	x	..	..	..	x	..	Excision	?	—
27	1933	..	..	x	6½	x	..	x	3½ yr.	..	..	..	x	x	..	..	..	..	Lysis	Trauma ?	..
28	1933	x	..	..	7	x	x	x	4½ yr.	..	x	..	..	..	..	x	..	..	Lobectomy	Birth injury ?	+
29	1936	x	..	..	7	x	..	x	2½ yr.	..	..	..	x	..	..	..	x	..	Excision	Trauma	+

AUTHOR: Is minus sign correct?

2 cases of porencephaly (cases 17 and 18), in which the patient was later subjected to radical excision.

COMMENT

The 29 patients treated by cerebral surgical methods form a small proportion of a group of epileptic patients from which they were selected. The choice of patients was dependent primarily on ability to demonstrate a localized lesion. A depressed fracture, focal convulsions, neurologic signs or pneumoencephalographic findings were the criteria of localization. The focal characteristics of the convulsions constituted the most helpful single factor in localization and were present in 25 of the 29 cases. The results of pneumoencephalographic examination were somewhat disappointing, being normal in 9 of 22 cases.

It must be admitted that the indications for operation are at present not entirely satisfactory. The absence of significant findings on exploration, though infrequent, has not been eliminated. On the other hand, in certain cases, in spite of a history of trauma, the patient has been denied the possible advantage of surgical therapy because of inability to localize the lesion. It appears likely that the electroencephalographic procedure may be an important diagnostic adjunct under these circumstances.

The importance of early operation is emphasized by the results in this series. In 7 of the 11 cases of cortical scar, satisfactory results occurred in patients whose convulsions had been present for not more than two years, while the failures in 4 cases were in patients having convulsions for more than two years. Similarly, in the group of degenerations, in 4 of the 6 cases in which the results were satisfactory the duration of convulsions was three years or less, while in 2 of the 3 cases of failure the duration was more than three years.

Surgical exploration of the cortex of patients with epilepsy presents a problem somewhat different from that encountered in patients with tumor of the brain. While many of the scars and some of the degenerative areas may be demonstrable by gross inspection or palpation, others are identified only by the results of electrical stimulation. This necessitates knowledge of such physiologic phenomena as inhibition, extinction, facilitation and spread of cortical stimuli. A minimal current should be used and a sufficient interval allowed between each stimulation. Any medication which may alter the threshold of cortical irritability, including general anesthesia, should be avoided. It is helpful to locate the precentral and postcentral gyri by their electrical responses early in the procedure. Other areas may then be accurately oriented with respect to these fixed points. The electrical production of a convulsion should be avoided until the last phase of exploration, since all

cortical responses may be abolished for a time after such a physiologic "explosion." When a convulsion is finally produced, its characteristics should be carefully compared with those previously experienced by the patient. Alterations in vascular characteristics of the brain before, during or after a convulsion should be noted.

Excision of pathologic areas in the cortex of an epileptic patient is based on the assumption that the convulsive symptoms are caused by the lesion. As a working hypothesis this is satisfactory, but the continuance of convulsions in some cases after surgical extirpation, as well as the fact that convulsions do not occur in all patients with similar lesions, indicates that other factors may be of considerable importance. The actual mechanism by which convulsions are produced is not entirely clear. It is unlikely that the abnormal neural activity actually originates within a scar. However, the junction of pathologic and normal tissue may act as the epileptogenic focus. Thus, electrical reproduction of convulsions occurs more readily when the stimulus is applied at the margin of a scar than when the scar itself is stimulated. Whether spontaneous convulsions are set off by traction of the scar on this marginal zone or whether a more indirect vascular effect is responsible remains to be determined. In either case, the situation necessitates complete extirpation of the area involved.

Consideration of the results in this series bears out the observation already mentioned that convulsions may continue after presumptive complete excision of the convulsive focus. In addition, there was considerable variation in the early response to this form of therapy. In some instances (cases 12, 13, 20, 23, 28 and 29) there was immediate and lasting relief from convulsive episodes. In 2 cases convulsions continued, decreasing in intensity and frequency up to seven (case 1) and twenty-one months (case 9), when the attacks disappeared. One patient (case 14) had frequent severe convulsions for several days after operation, followed by complete relief. Others showed immediate favorable results, only to lapse into mild (cases 11 and 21) or severe (cases 17, 18 and 27) attacks after a year or more. Still others (cases 3 and 4) experienced gradual improvement over a number of years. The recurrence of convulsions after a period of initial relief might be interpreted in terms of a recurrent scar. However, many factors lead to the assumption of a basic convulsive tendency which may still be present after the irritative focus has been removed. Thus, a convulsive episode may occur during a febrile illness or other systemic disturbance after months or years of freedom. As this paper was being prepared, 1 patient (case 16) reported that he had had an isolated convulsion on the occasion of his mother's death, which necessitated a change in his status from that of a "successful result" to "improvement."

Comparison of the pathologic lesions in this series indicated some similarity between the three groups. Glial proliferation was not uncommon in the degenerative lesions and differed chiefly in degree from that observed in the true glial scars. Glial elements were likewise present in the fibrous scars, while true glial scars were seen in the walls of porencephalic cavities. The recent work of Evans [3] indicated that experimental occlusion of cerebral arteries may result in the formation of a cortical cicatrix when the vascular deficit is partial, or of porencephaly when it is complete. With regard to the degenerative lesions: It is difficult to state with certainty that the pathologic changes may not be an effect rather than a cause of convulsions. However, the failure to demonstrate such changes in specimens of the cortex taken for biopsy from other epileptic patients suggests that a causal relationship is present.

SUMMARY AND CONCLUSIONS

1. Analysis of 29 cases, after intervals of from one to eight and a half years following cerebral surgical procedures for treatment of epilepsy, revealed satisfactory results in 19 cases, in 10 of which there was complete relief from convulsions and in 9 definite improvement. There were 9 failures and 1 death. The cases were grouped on the basis of three types of pathologic lesions: scars, 16 cases; porencephaly, 4 cases, and degenerations, 9 cases.

2. There appeared to be a definite correlation between duration of convulsions and prognosis. The results obtained with patients whose convulsions had been present for less than two or three years were much better than those with patients whose convulsions had occurred over a longer period.

3. The pathologic lesions ranged from simple degeneration of ganglion cells, through degeneration with glial proliferation, to dense glial or fibrous scars. Definite glial scars were seen in the walls of porencephalic cavities.

ABSTRACT OF DISCUSSION

DR. R. G. SPURLING, Louisville, Ky.: I wish to emphasize the statement that each patient should be subjected to careful medical treatment before operation is contemplated. By adequate medical treatment I mean drug therapy, pushed to the limit of tolerance, and careful dietary management. When the medical routine has been followed for a reasonable time and has failed, one can evaluate correctly the result of the surgical procedure, for all patients must have postoperative medical treatment. I have observed repeatedly patients with focal grand mal epilepsy, with or without abnormal encephalograms, become completely free from symptoms with medical treatment alone.

3. Evans, J. P.: The Anatomical End Results of Cerebral Arterial Occlusion: An Experimental and Clinical Correlation, Tr. Am. Neurol. A., to be published.

My experience with air studies has been somewhat different from Dr. German's. I have never demonstrated surgically scarring of the cerebral cortex without having seen local evidence of disease in the encephalograms. The changes in some cases have been slight; however, when correlated with the clinical picture they became understandable. By slight encephalographic changes I mean abnormalities in the distribution of the cortical air or in the markings of the hidden convolutions, changes in the basal cisterns or local dilatation or displacement of the ventricular system.

Dr. German is correct when he says there is usually a correlation between duration of convulsions and prognosis. However, exceptions to this rule often provide one with gratifying results. One of my patients, aged 28, had had severe focal fits since birth. After removal of a large postcentral scar, he has had no semblance of an attack for three years.

Dr. William J. German, New Haven, Conn.: I am glad that Dr. Spurling emphasized the importance of an adequate test of medical therapy before resort to surgical treatment; I think one must include diphenylhydantoin.

Concerning the encephalographic findings: I admit that when one reviews the encephalograms after verifying the lesion one can occasionally see changes at the site of the lesion. I wished merely to emphasize in the paper that the encephalograms may not be convincingly diagnostic.

The favorable results which Dr. Spurling had in 1 case in which epilepsy was of long standing may be gratifying, but they should not make one too optimistic.

STUDIES IN MONGOLISM

I. GROWTH AND PHYSICAL DEVELOPMENT

CLEMENS E. BENDA, M.D.
WRENTHAM, MASS.

The clinical picture of mongoloid deficiency is so well known that there is no need to deal with it at length or to enumerate the many isolated findings recorded in the literature. Since Langdon-Down [1] in 1866 called attention to the various physical features in idiocy, when he first used the name of "mongolian imbecility," many publications in different languages have been concerned with this disease.[2] T. Smith, Sutherland, Shuttleworth, Tredgold and Brousseau, in English; Vogt, Weygandt, F. Siegert and Kassowitz, in German; Bourneville, Comby and his pupils, in French, and Cozzolino, in Italian, dealt especially with mongoloid deficiency and laid the foundation of knowledge of this peculiar condition. These papers contain many observations and particular findings, but no real attempt has been made to reach a point of view by which it would be possible to correlate the scattered findings with one cause or a group of causes.

The following problem suggested itself after I began to study the mongoloid defective. Other constitutional defects and psychoses do not obliterate the individual differences due to race and family. Even idiots vary as much from each other in appearance as normal persons. How does it happen that mongoloid children have such similar faces and are so much alike that most of them look like brothers and sisters? Does mongolism represent a "mutation" and formation of a special race, even one so pathologic, through a change in the germ plasma, or is it a disease? If the latter is true, what can produce such a similarity of features in different persons, and at what time must this cause be active?

The physical characteristics of mongolism cannot be the result of the idiocy or of any mental defect. One should study rather the problem of a possible somatic basis for this form of feeblemindedness and ask the question: "How may the physical feature be related to the mental con-

---

From the Research Department for the Study of Mental Deficiency, Wrentham State School, and the Department of Neuropathology, the Harvard University Medical School, Boston.

1. Down, J. L.: Observations on an Ethnic Classification of Idiots, Clin. Lect. & Rep. London Hosp. **3**:259, 1866.

2. See bibliography in Brousseau, K.: Mongolism: A Study of the Physical and Mental Characteristics of Mongolian Imbeciles, Baltimore, Williams & Wilkins Company, 1928.

dition?" The many publications dealing with the characteristics of mongolism, such as the fold of the eyes and the size of the hands, the feet and the tongue, are contradictory with regard to the question of which stigmas are essential and which are not. One reason for this discrepancy seems to be that most authors studied mongolism indiscriminately, without regard to differences in age.

In order to gain further insight into the nature of mongolism, I started a series of investigations with special consideration of the time factor in this disease. These studies included a clinical analysis of the mongoloid appearance, with clinical measurements, roentgenograms and postmortem examinations, the results being classified according to the age of the patient.

It is well known that the diagnosis of mongolism can be established at birth or a few days after birth. It is beyond the limits of this paper to discuss to a great extent the diagnosis of mongolism. In determining what establishes the diagnosis of mongolism at birth, the slanting eyes, which are often emphasized, or the epicanthal folds do not seem fundamental. Only one third of mongoloid children are said to have real epicanthal folds at birth (Siegert); on the other hand, many pediatricians stress the fact that epicanthal folds are not unusual in the first years of life, especially in some localities. Even the slant of the eyes is not always striking, and markedly slanting eyes without the slightest relation to the mongoloid condition are not rare (fig. 1 *A* and *B*). Clinical examinations led to another point of importance. I found that all the peculiarities of the mongoloid appearance are related to a particular formation of the skull. Comparison of the skull of a normal newborn infant and that of a mongoloid child showed that they are different. The forehead of an infant with mongolism appears much higher and broader than that of a normal newborn child. The frontal bosses are prominent. The eyes are protruding, and the palpebral fissure appears more or less slanting; more important, however, is the fact that the orbital cavity appears small in relation to the eyeballs and that the distance between the orbits is less than is normal. The face is flat. With every week after birth the mongoloid appearance becomes more striking. The orbital line is rounder than is the normal. The lateral and medial margins of the orbit lie in the same plane, whereas in the normal the lateral margin of the orbit is placed posteriorly in relation to the medial margin. The orbital angle formed by the zygomatic process of the frontal bone and the frontal process of the zygomatic bone is wider than is normal. It is this malformation which gives the flat, simian appearance to the eyes. In later life the animal-like appearance is sometimes accentuated by a fold of skin on the external margin of the eye. The skull is not microcephalic at the time of birth.

The formation of the bridge of the nose is also typical in mongoloid patients. The nasal bones are small and sunken. In mongoloid adults

the cartilaginous part of the nose is more prominent, and therefore the saddle nose associated with mongolism is different from that characteristic of congenital syphilitis.

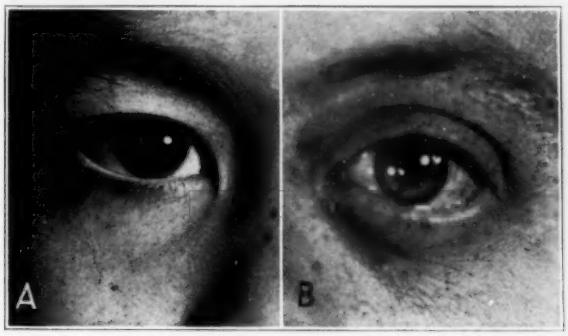


Fig. 1.—*A*, eye of a boy with Mongolian characteristics, showing a marked epicanthal fold and slanting. The eye is full of expression, and the skin is elastic and of fine texture. There is no relation to mongoloid deficiency. *B*, eye of a girl with mongolism. The eyeball is more protruding than that shown in *A*. Note the thickness of the eyelids and the folds of skin at the lateral margin. There is no epicanthal fold or slanting of the eyes, although the patient presents one of the most marked cases of mongolism.

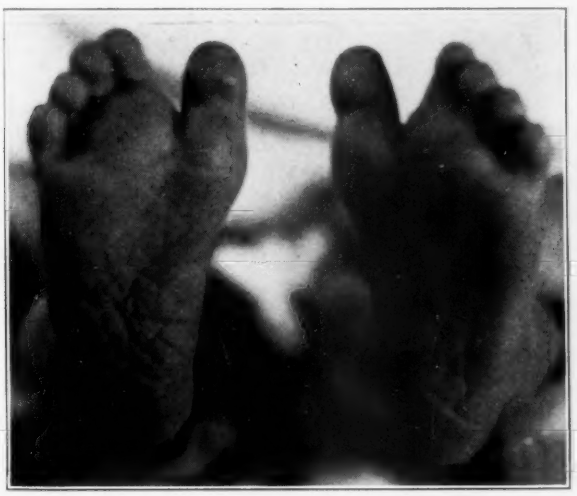


Fig. 2.—Feet of an 11 day old mongoloid infant. Note the deep gap between the big toe and the second toe and the wrinkling of the skin.

In addition to the skull, the hands and feet may be suggestive of the correct diagnosis (fig. 2). The skin is more wrinkled than that of the normal newborn child; the wrists especially show an excessive

Age, Mo.	Case	Sex	Height		Weight, Lb.	Length of Skull, Cm.	Width of Skull, Cm.	Circumference of Skull		Sexual Development
			Cm.	Inches				Cm.	Inches	
2	1	M	45	17.75	7.5	12.4	9.8	36.4	14.5	
3	2	F	59.8	23.5	8.8	11.6	10.8	36.5	14.6	
5	3	F	59	23.25	10.2	12.6	11.8	39.2	15.6	
5	4	M	56.5	22.25	9.4	12.5	11.2	37.3	14.12	
7	5	F	65	25.5	11	13	10.5	38.3	15.3	
13	6	F	75.4	29.75	22	13.6	11.7	41.8	16.8	
Yr.										
2	7	F	79	31	25	13.5	12.9	44.6	17	
2	8	M	83.2	32.75	19.75	12.7	12.5	48	18.14	Testes not descended
2	9	M	80	31.5	25	13.8	13.7	46	18.2	Testes not descended
3	10	F	87.5	34.8	28	14.8	12.9	45.4	17.14	
3	11	F	84	33	23	15.4	12.6	44.5	17.9	
4	12	F	86	33.75	34	15.2	13.8	46.2	18.3	
4	13	F	96.2	37.75	31	16.2	13.4	48.5	19	
4	14	F	92	36.25	29	15.5	12.3	44.8	17.12	
4	15	F	93	36.75	40	14.8	14.8	47	18.8	
5	16	F	97	38.25	38	15.8	13	45.9	18.2	
5	17	F	89.5	35.25	36	16.2	13.9	49.9	19.1	
5	18	M	98.8	38.75	34	17	13.4	47.6	18.1	Testes not descended
5	19	M	86.5	34	32	15.1	13.1	46.3	18.4	
5	20	M	81	32	28	13.5	1.3	44	17.4	
6	21	F	106	41.75	46	15.5	14.3	48	18.14	
6	22	F	97	38.25	36	15.9	13.3	46.5	18.4	
6	23	F	100	39.10	37	15.8	13.1	46.3	18.3	
6	24	M	109.5	43.6	56	15.5	14.7	48.5	19	Testes not descended
6	25	M	107	42	36	15.2	13.5	44.6	17	One testis descended
6	26	M	99	39	42	16	13.5	47	18.8	One testis descended
7	27	F	100	39.10	37	15.3	13	45.6	17.15	
7	28	M	117	46	54	16.5	14	50	19.1	
7	29	M	108	42.5	47	16.3	13.4	48	18.14	Testes not descended
7	30	M	108	42.5	41	16.1	13.7	48.6	19.1	Testes not descended
7	31	M	119.5	47	51	16.3	13.7	48	18.14	Testes not descended
7	32	M	109.5	43.2	41	15.5	12.4	44.7	17.11	
7	33	M	110.5	43.5	42	15.8	13.9	48	18.14	Testes not descended
7	34	M	117	46	49	15.7	13.4	46.4	18.4	
8	35	F	103	40.5	42	16.5	13.5	48.5	19.2	
8	36	F	109.5	43.5	39	15.1	13	45	17.12	
8	37	M	117	46	52	15.9	14.5	48.5	19.2	
8	38	M	112.5	44.25	48	16.9	14.7	50.1	19.11	Testes not descended
9	39	F	125.5	49.7	59	16.5	14.2	49	19.5	
9	40	F	109	43	41	14.8	13.2	45.8	18.1	
9	41	F	104	41	37	15.5	13.2	46.8	18.17	
9	42	F	104.5	41.3	40	14.5	13.4	45.5	17.15	
9	43	F	126	49.5	51	16	14	48.5	19.2	
9	44	F	106	41.75	41	15.6	13	46.5	18.5	
9	45	F	121	47.1	56	16.5	13	47.7	18.13	
9	46	F	105.5	41.5	39.5	15.8	13.3	46.4	18.4	
9	47	M	117	46	51	15.8	14	48.5	19.2	One testis descended
9	48	M	118	46.5	52	15	14.2	46	18.2	
10	49	F	126.5	49.75	69	15.4	13.8	47.5	18.12	
10	50	F	120	47.25	52	16.4	13.3	47	18.8	
10	51	M	120	47.75	52	15.1	15	48.6	19.2	Testes not descended
10	52	M	129	50.75	60	15.7	14.6	48.7	19.3	Testes not descended
10	53	M	111.5	44	68	16.9	14.2	49	19.5	One testis descended
10	54	M	129.2	50.14	64	15.6	13.4	47	18.8	
11	55	F	123	48.5	53	16.8	13.2	48	18.14	
11	56	F	128.5	50.1	69	16.2	13.9	49.5	19.8	
11	57	F	123.3	48.9	69	16	13.5	46	18.2	
11	58	M	139.5	55	70	17.4	13.7	48.5	19	
11	59	M	128.5	50.1	58	15.8	13.8	47.5	18.9	
11	60	M	127.7	50.25	76	16.6	14.1	49	19.5	
11	61	M	124.5	49	61.5	17.4	13.8	49.4	19.7	
11	62	M	124.5	49	54	17.7	14.2	49.5	19.8	Testes not descended
12	63	F	133	52.6	72	16.7	13.8	49.3	19.6	
12	64	F	124.6	49	53	15.9	13.2	46.7	18.5	
12	65	M	136	53.9	76	18.5	14.5	53.8	21.3	One very small testis
12	66	M	120.5	47.5	58	16	13.7	49	19.5	
12	67	M	150	59	71.5	16.4	14.6	50.5	19.15	
13	68	F	137	54	88	16.4	15	49.8	19.1	
13	69	M	136	53.9	78	16.5	14.4	50.5	19.15	Testes not descended
13	70	M	131	51.5	62	15	14.4	48	18.14	
13	71	M	137.5	54.9	77	17.8	13.8	50.5	19.15	
13	72	M	124	48.13	66	14.9	13.1	45.6	17.15	Testes not descended

Clinical Data in 120 Cases of Mongolism—Continued

Age, Yr.	Case	Sex	Height		Weight,	Length of Skull,	Width of Skull,	Circumference of Skull		Sexual Development
			Cm.	Inches	Lb.	Cm.	Cm.	Cm.	Inches	
14	73	F	142	56	93	16.1	14.5	49	19.5	
14	74	F	141.5	55.75	78	17.5	13.4	49.5	19.7	
14	75	F	141	55.5	98	16.5	13.7	49.2	19.5	
14	76	F	135.5	53.6	90	17	13.8	48.7	19.3	Irregular menses
14	77	F	133	52.6	70	15.3	14.4	46.5	18.5	No menses
14	78	F	136	53.9	95	16.7	14.2	50	19.1	
14	79	F	140	55.1	80	16.5	13.6	48.5	19.2	
14	80	M	129.5	51	82	16.6	14.4	50.5	19.15	
14	81	M	135.5	53.6	74	16.7	14.9	50.3	19.13	
14	82	M	137.3	54	84	16.5	13.9	48.6	19.2	
15	83	F	145.5	51.5	99	16.8	14.3	49.2	19.5	
15	84	F	134	52.75	78	16	14	48	18.14	No menses
15	85	F	130	51.25	109	17	14.8	50.5	19.15	
15	86	M	123.5	48.1	81	17.3	14.5	51	20.1	
15	87	M	139	54.75	101	17.2	14.3	50.5	19.14	Small testes
16	88	M	160	63	129	18	15.1	53.5	21.1	Small testes
17	89	F	145	57.2	83	16.4	13.3	49	19.4	Irregular menses
17	90	F	135	53.3	105	16.9	13.4	49	19.4	
17	91	F	146	57.5	105	17	14.8	50.8	20	
17	92	M	151	59.1	126.5	17.3	14.8	51	20.1	
18	93	F	142	56	98	16.9	14.3	53	20.14	
18	94	M	152.5	60.1	102	17.7	14	51	20.1	
18	95	M	151	59.7	127	17	14.3	50.5	19.14	
19	96	F	144	56.75	93	17.2	14.7	50.6	19.15	
19	97	M	148.5	58.8	109	16.9	14.2	49.3	19.5	
19	98	M	148.2	58.6	124	17	16.5	51	20.1	
20	99	M	157	61.13	116.5	16.7	15	55.1	20.1	
21	100	F	135.5	53.6	104	17.5	14.6	50.7	19.16	
21	101	F	126	49.1	98	16.1	14	49	19.4	Irregular menses
21	102	M	152	59.14	137.5	17	14.5	51.5	20.4	Very small testes
22	103	F	137.5	54.3	84	17.5	15	49.4	19.6	
22	104	F	140	55.8	118	15.8	14.2	49	19.4	
22	105	M	152.5	60.1	111	18	14.6	52	20.8	
22	106	F	134.4	52.13	90	16	14	48.6	19.2	Regular menses
23	107	F	131	51.1	90	16.2	14.4	49.2	19.5	
23	108	M	143	56.25	130.25	18.4	15.7	52	20.8	
23	109	M	149	58.12	98	16.1	14.7	50	19.1	
23	110	M	157.5	59	136	18.2	14.4	53.4	21.1	
23	111	M	149	58.12	114	17	15	51	20.1	Very small testes
24	112	F	138.5	54.9	92	16.7	15.2	49.6	19.7	
25	113	F	136	53.9	99	17.2	13.5	49.7	19.8	
25	114	M	141	55.5	99.75	17	15	50.7	19.16	
27	115	M	157	61.13	134	16.7	14.3	51.7	20.5	One testis descended
28	116	M	143	56.25	138	17.2	15.3	50.5	19.14	
28	117	F	141	55.25	106	17.2	14.5	51	20.1	
28	118	F	148	58.5	104	15.5	13.8	47.5	18.9	
33	119	F	143.6	56.5	98	16.6	13.9	50.7	19.16	Regular menses
34	120	F	138.5	59.4	94.5	16.7	13	49.5	19.8	No menses

amount of wrinkling. The palmar lines are more marked. Between the big toe and the second toe there is nearly always a deep gap. The fingers appear short and broad in later life. The little finger shows marked curvature. The thumb and little finger appear much shorter than those of a normal child. The height and weight do not differ from those of the normal newborn child.

In order to gain more exact information in regard to the formation of bone and the development of the mongoloid child, I carried out determinations of the height, weight and length, width and circumference of the skull. In each case, these measurements were associated with a neurologic examination, but in what follows I wish to call attention

especially to the problem of the formation of the skull and the growth in general. The accompanying table gives information in regard to growth in cases of mongolism.

My measurements show that at birth the height of the mongoloid child is within the limits of the normal. The length of the body of some mongoloid infants is at the lower level of the normal, but that of others is at the higher level. At the Children's Hospital at Boston I examined records of mongoloid patients in the first months of life in order to increase the number of measurements and found similar conditions in these children, as illustrated in the following tabulation.

Age	Height, Cm.	Age	Height, Cm.
9 days	46	9 mo	65
6 wk	49	13 mo	70
3 mo	52	18 mo	72
6½ mo	60		

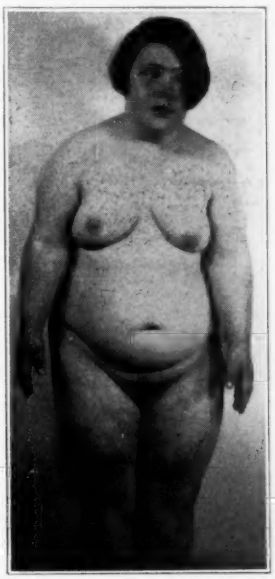
The height of children with mongolism slowly increases in the first five years, but is still at the lower level of the normal. At the age of 6 years the height of a child should exceed 100 cm. That of most mongoloid children does. At 7 years of age small progress is recognizable. From 8 years on the retardation becomes increasingly apparent, and at the end of the period of growth few persons with mongolism exceed 150 cm. in length of body. Only 8 boys in my material reached a height of over 150 cm.; it is interesting that these boys represented borderline cases, with only some mongoloid stigmas. No mongoloid girl exceeded the height of 150 cm.

Conversely, the weight at birth and during the first year is lower than the normal. During the following three years the weight is within the normal limits. At the age of 5 years the increase in weight becomes more noticeable, and most mongoloid children are overweight after that time. This is especially striking when the weight is compared not with that of a normal child of average height, but with that of a child of the same length. Many adult persons with mongolism, especially women, appear to be of the "dystrophia adiposogenitalis" type" (fig. 3). Only a few mongoloid adults are underweight. They frequently show pituitary cachexia.

Measurements of the skull show that at birth the circumference is within the limits of the normal. The normal skull increases approximately 10 cm. in circumference during the first months of life. The amount of growth in this period is remarkable. The mongoloid child cannot keep pace with this rate. After 6 months all children with mongolism appear microcephalic, and in two years the skull reaches a circumference which should be attained within the first year. The mongoloid patient is not able to compensate later for this failure of growth. This is especially interesting when one compares the growth of

the skull between the ages of 5 and 20 years. The normal skull gains about 1.2 cm. in width in these fifteen years, starting at the width of about 14 cm. and reaching at least 15.2 cm. The mongoloid skull increases by about the same amount in this period, but it starts at a lower level, at about 13 cm., and reaches a width of about 14 or 15 cm. in the adult.

The length of the skull normally increases from 17.6 to 19.3 cm. during the same period. Between the ages of 5 and 20 years the mongoloid skull grows from about 15.5 to 16.8 cm.; that means an increase in length of about 1.3 cm. This is only a little less than the normal increase



Figi. 3.—Mongoloid woman. Dystrophia adiposogenitalis is frequently seen in mongoloid persons after puberty.

and would be sufficient if it started at the same point; actually, the length of the skull at the age of 5 years is 15.5 instead of 17.6 cm.

These facts are of importance for many reasons. The study of growth showed that the mongoloid child increases in stature during the first seven years of life; during these years he seems not to differ markedly from a normal child in physical development. A mongoloid child between the ages of 3 and 10 years appears healthy, except for the peculiar formation of the skull (fig. 4). After the first ten years development becomes progressively retarded, and most persons with mongolism do not show further growth after the age of 14. The growth of the mongoloid adult is arrested earlier than that of the normal person.

At first sight the development of the skull appears to differ, but later analysis will show that one is dealing with the same pathologic process.

In order to gain more exact information in regard to the growth of bones, roentgenographic examinations were made of the skulls of 20 mongoloid patients of different ages and of the hands of 29.

Roentgenographic examination of the carpal bones is an excellent method of testing the degree of ossification. The time of appearance of the centers of ossification is well known. Ossification of the carpal bones appears successively over a period of about fourteen years. Demonstration of the bones of the hand is a standard method of comparing the progress of ossification at different ages in cases of cretinism and

Fig. 4.—Mongoloid children. From left to right, the ages are: 4 years and 10 months; 3 years and 10 months; 9 years, and 6 years.

myxedema in childhood. Recently, J. H. Means stressed the importance of this means. However, it has received little attention in investigations on mongolism. Siegert alone emphasized the value of this examination in cases of mongolism. Brousseau also mentioned the method, but referred only "to an evident irregularity in the time of ossification," without giving more exact information on the number and details of observations.

My roentgenographic examinations[3] of mongoloid patients have shown that the first appearance of centers of ossification in the carpal

3. A more extensive study of this matter will appear in another paper, entitled "Clinical and Pathologic Studies in Mongolism," read before the Boston Society of Psychiatry and Neurology, Nov. 17, 1938.

bones is often premature. It is noteworthy that in most mongoloid children the centers of ossification of the hamate and capitate bones appear before the sixth month of life. Ossification of the pisiform bone was present in 1 case at the age of 6 years, and in nearly every case between the ages of 6 and 10 years all the centers of the carpal bones were observed. Between the ages of 2 and 14 years, the findings corresponded to a normal state of development in several cases. Retardation was not found; that is noteworthy, as all other organs show marked retardation. The definite ossification, especially fusion of the epiphysial lines, is always premature. All bones of the arms and hands of mongoloid patients show complete ossification at the age of 17 years. Roentgenograms of the pelvis reveal premature fusion of the sutures.

Much emphasis was placed on the study of the formation of the skull. It may be well to describe the observations at autopsy before entering into a discussion of the roentgenographic findings, for only the anatomic study gives sufficient material for correct interpretation of the roentgenograms.

I had the opportunity of studying the formation of the skull at autopsy in 10 cases of mongolism; the anatomic changes were so definite that I feel safe in stating that the mongoloid appearance is correlated with malformation of the base of the skull.

The anterior cavity in cases of mongolism is characterized by extreme protrusion of the roofs of the orbits. Slight projection of the roofs is normally observed, but in patients with mongolism they form a marked protuberance. The cribriform bone is short and retracted and forms a small, deep valley between the arches of the orbits. Another peculiarity of the roofs of the orbits is that they ascend laterally toward the frontal bone without leaving any deepening between the top and the facies temporalis of the frontal squama. That gives the anterior cavity as a whole a curved shape, the floor sloping upward anteriorly and laterally toward the frontal bone. The sphenoid bone is small and the body of the bone underdeveloped. It is noteworthy that neither a frontal nor a sphenoid sinus is to be seen in cases of mongolism. Although these sinuses are not fully developed before the seventh year of life, slight pneumatization is noticeable several times before that age, and comparison of the normal body of the sphenoid bone and that in cases of mongolism reveals that the latter is underdeveloped.

The middle cavity appears deep and is overshadowed by the projecting major wings of the sphenoid bone. The posterior cavity shows typical signs. The occipital squama is steep and upright, instead of lying in a rather horizontal position behind the foramen magnum. Sometimes the occiput slopes in a way that continues the line of the spine. The foramen magnum in several cases was observed to be small and transversely ellipsoid, showing so-called frontal stenosis.

On the whole, the shape of the base of the skull, especially the posterior cavity with its steep occiput and the anterior cavity with its protruding orbit roofs, ascending toward either side, with the small, retracted cribriform bone and underdeveloped nasal bone, gives the mongoloid skull such a typical appearance that the diagnosis may be established with a high degree of assurance.

The question arose whether these anatomic observations can be utilized for establishing the diagnosis by roentgenographic examination in doubtful cases. Accordingly, roentgenograms of the skull of 20 mongoloid patients were made. The lateral view of the mongoloid skull reveals the short, retracted cribriform bone and the marked underdevelopment of the nasal bone. The roofs of the orbits are protruding and abnormally situated in relation to the facial bones. Noteworthy is the smallness of the sphenoid body. The steep occipital squama is readily recognizable. A posteroanterior view adds to the previous observation an important fact. In a normal skull the supraorbital notch indicates the highest point of the supraorbital margin. Laterally, the margin curves downward and articulates at its external end with the upstanding frontal process of the zygomatic bone. In the mongoloid skull the supraoccipital border follows an upward curve toward the external end, forming at this point a rather sharp angle with the zygomatic process. Therefore, in cases of mongolism the supraorbital notch does not represent the highest elevation of the upper orbital margin. As a matter of fact, the slanting eyes of patients with mongolism are caused by slanting orbital openings. A study of the upper orbital margin in cases of mongolism indicates the deformity of the skull and is suggestive of the diagnosis of mongolism. The Mongolian race does not show such an upward curvature of the orbital margin. Lack of formation of the frontal sinus is easily recognizable in the anteroposterior view of the skull of a mongoloid child after the seventh year.

In order to understand this condition, I must refer to the embryonic development of the skull. The envelop of the brain is formed by two types of bone: cartilaginous and membranous. The occipital bone (except the os interparietale) and the sphenoid and ethmoid bones are developed from cartilaginous tissue. The interparietal, the parietal, the frontal and the temporal bone are ossified in the membranous envelop of the brain.

In analyzing the disorder in mongolism, one finds that primarily the cartilaginous bones are affected. There is a disorder in the proliferation and ossification of the cartilaginous bones.

In the carpal and the long bones, I found that ossification is early and that growth of the bones comes to an early end. One sees now that at the base of the skull also, the cartilaginous bones show lack of proliferation and irregularity in ossification. The result is that the base of the skull

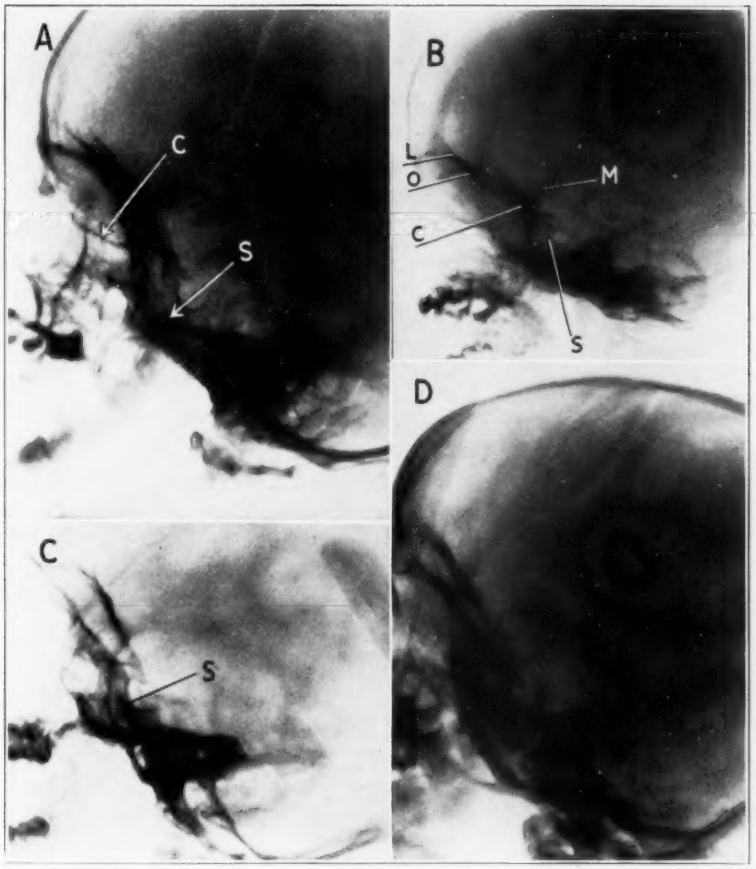


Fig. 5.—Roentgenograms of the skull. *A*, the skull of 5 year old child, with a normal base. Note the development of the sphenoid bone (*S*), the body of which is large. Later the sphenoid sinus will appear at this place. The cribriform bone (*C*) shows already rather a horizontal position. The upper margin of the orbits is markedly curved.

B, skull of a 7 month old mongoloid boy, taken before autopsy. The circumference of the head is 14.12 inches (35.8 cm.); the length of the skull, 12.6 cm., and the width, 10.7 cm. *S* indicates the sphenoid bone; *C*, the cribriform bone; *O*, the roof of the orbit; *L*, the lateral edge of the anterior fossa, and *M*, the meningeal groove.

The sphenoid bone and the sella are small; the cribriform bone is short and retracted. The nasal bone is poorly developed. The roofs of the orbits protrude into the anterior cavity. The bottom of the anterior cavity forms a steep slope, which is elevated toward the front and the lateral edge. The cribriform bone is deeply depressed. Note the distance between the cribriform bone and the roof of the orbits.

C, skull of a 5 year old mongoloid boy. Note the smallness of the sphenoid bone and the upright position of the sella turcica.

D, skull of a 4 year old mongoloid girl. The length of the skull is 14.8 cm.; the width, 14.8 cm., and the circumference, 18.8 inches (47.7 cm.). Note the smallness of the sphenoid bone. The anterior cavity of the skull is short and the floor is sloping.

remains proportionately smaller than normal and retains a formation seen during the first months of embryonic development. The further development of the normal skull, consisting in growth and molding of the base, is interrupted. Pneumatization is lacking.

The membranous bones are much less affected than the cartilaginous bones. Therefore the latter show slight increase in size and development during later life. One understands now a contradiction frequently

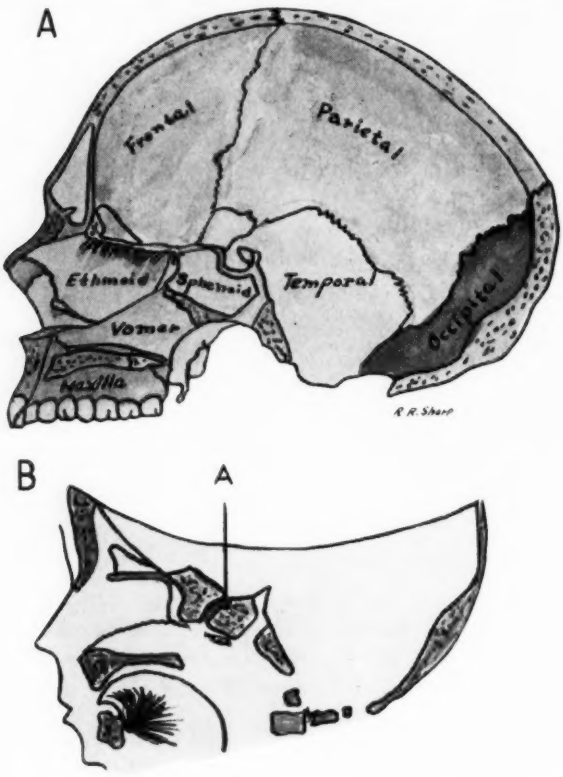


Fig. 6.—*A*, skull of a normal adult (drawing after Gray's "Anatomy"). Note the horizontal line of the anterior part of the sphenoid bone and the cribriform plate and the distance between the anterior clinoid process and the frontal bone. The sella turcica is in a rather horizontal position.

B, skull of a 1 year old child (drawing after Virchow, 1857). The sphenoid bone is still separated by cartilage (*A*). Virchow demonstrated that during ossification of the cartilage the anterior part of the sphenoid bone moves down and the bottom of the anterior cavity becomes a rather horizontal plane, parallel to the palate.

appearing in the literature. In mongoloid children closure of the fontanels is usually retarded, and the fontanels are larger than in normal children. Many authors were unable to understand how the early ossi-

fication of some bones corresponds with retarded closure of the fontanels; closure of the fontanels, however, is due to proliferation and ossification of membranous bones, whereas the base of the skull is formed by cartilaginous bone.

With regard to the later increase in size of the skull: One sees that the early ossification of the base limits the growth. Increase in width is more possible, owing to the membranous formation of the temporal and parietal bones. Indeed, the skull of the mongoloid patient shows a more marked increase in width, which corresponds nearly to that in normal children. Increase in length is more limited, and the skull becomes progressively brachycephalic, for the occiput does not participate in the growth.

From a historical point of view it is of interest that Virchow [4] in 1858, recorded 3 cases of "cretinism" in which he proved that premature ossification of the base, of the "os tribasilaris," was present. He concluded that this gave rise to the peculiar appearance of cretins. Virchow demonstrated impressively that the possibility of growth of the skull in different directions is dependent on long persistence of the sutures and cartilaginous spaces. If there is lack of cartilage through premature synostosis, there is no possibility for the bones to grow, and a deep-set nose, protruding forehead and malformation of the orbit appear.

Bayon [5] refuted Virchow's statement with great emphasis, demonstrating that premature ossification cannot play an important role in cretinism. At this time the cause of cretinism was well established. Cretinism was proved to depend on athyroidism or hypothyroidism. Retarded ossification and persistence of the cartilaginous spaces could be demonstrated in all classes of cretinism. Bayon was undoubtedly right when he refuted Virchow's statements about cretinism, but at the time of Virchow's investigations no difference between cretinism and mongolism was known. I think that it is not correct to regard Virchow's observations as mistaken. Remarks in his paper prove that he was conscious of dealing with different forms of "cretinism"; he distinguished at least two, and probably three, types. He stated (page 335) with regard to one type of cretins that in the various populations a close kinship of the whole organization is recognizable, so that one may believe that cretins are remnants of a population now disappeared, which was organized on a lower level and had degenerated.

Weygandt [6] reexamined one of Virchow's specimens and concluded that Virchow was dealing with a case of chondrodysplasia.

---

4. Virchow, R.: Knochenwachsthum und Schädelform, mit besonderer Rücksicht auf Cretinismus, Virchows Arch. f. path. Anat. **13**:323, 1858.

5. Bayon, P. G.: Ueber angebliche verfrühte Synostose bei Kretinen und die hypothetischen Beziehungen der chondrodystrophia foetalis zur Athyreosis, Beitr. z. path. Anat. u. z. allg. Path. **36**:119, 1904.

6. Weygandt, W.: Ueber Virchow's Kretinentheorie, Neurol. Centralbl. **23**: 290, 1904.

Since that time knowledge of the ossification and growth of bones has greatly increased. It is known that not only ossification but proliferation of the cartilage and bone tissue plays an important role in the transformation of cartilage into bone.

The malformation of the skull in mongolism resembles in some points that of chondrodysplasia, but in chondrodysplasia only the base of the skull is affected and the vault does not participate in the disorder. The vault of the chondrodysplastic child is large, and the circumference may even be normal. In cretins, also, the vault is normally developed, and the skull is usually larger in circumference than normal. In cases of chondrodysplasia, intelligence does not participate in the disorder. Therefore, the disturbance associated with mongolism is much more complicated than that with chondrodysplasia or cretinism, and the different pathologic processes should be carefully distinguished.

SUMMARY

Clinical examination of 120 persons with mongolism has shown that the condition is present at birth. Therefore, the influence which leads to the condition of mongolism is predominant during the prenatal period. After birth there are residuals of such an influence, and one finds remarkable retardation in development. Many mongoloid children die in the first years of life. If the child survives the first few years, he adjusts himself fairly well to the biologic conditions of life.

Measurements on 120 persons with mongolism have shown that growth is slow but at a low normal level during the first nine years. Increase in height ceases early, and after the fifteenth year few mongoloid persons show further growth. Most do not reach a height of 150 cm. During the first two years of life, mongoloid children are usually underweight. After the fifth year many become overweight, and dystrophia adiposogenitalis is frequent after puberty.

The mongoloid skull is not microcephalic at birth, but shows lack of growth, which is especially apparent during the first six months of life, in which time the normal skull increases about 10 cm. The mongoloid child cannot keep pace with this rate. After six months all mongoloid children appear microcephalic. Compensation for the failure of growth which occurs in the prenatal period and during the first months of life is never possible. It has been demonstrated that the lack of growth is due to early arrest in the development of the base of the skull. The increase in length of the skull, therefore is especially limited. The peculiar shape and appearance of the skull associated with mongolism are due to the abnormal position and configuration of the base and the orbits. This deformation is in some points similar to changes associated with chondrodysplasia, but in persons with mongolism the fibrous parts of the

skull participate in the general disturbance of growth. Such persons show microcephaly and brachycephaly, whereas chondrodysplastic children and cretins have large vaults.

Irregularity of ossification was demonstrated by roentgenographic examination of the carpal bones. Persons with mongolism usually show early ossification and fusion of the epiphysial lines, even when the condition is complicated by rickets.

The investigation has proved that mongoloid deficiency is not a racial mutation but the result of a disturbance which becomes apparent during fetal development. The mongoloid appearance is due to a peculiar formation of the skull and has nothing to do with the Mongolian race or any kind of atavistic regression.

CEREBRAL ARTERIOSCLEROSIS

SIGNS AND SYMPTOMS FROM COMPRESSION AND EROSION OF PARENCHYMATOUS TISSUE

N. W. WINKELMAN, M.D.
PHILADELPHIA

My object in this paper is to show that sclerotic blood vessels in the brain at times so press on and actually excavate the adjacent parenchymatous tissue that clinical pictures are produced resembling those of focal lesions. In the course of study of the pathologic changes in many cases of cerebral arteriosclerosis my colleagues and I were struck by the fact that in a small number the blood vessels acted as minute expansile lesions. We saw in some instances actual erosion of brain tissue, so that eventually a small groove was formed by the sclerotic, tortuous and frequently enlarged blood vessel at the expense of the functioning structure of the brain.

This condition has not been entirely overlooked in the literature, since reference to it has been made particularly in conjunction with pressure on cranial nerves. Pappenheim,[1] in 1926, claimed that trigeminal neuralgia can be caused by pressure of a sclerotic blood vessel against the fifth cranial nerve. Dandy,[2] in an article explaining the mechanism of trigeminal neuralgia, expressed the belief that in 30.7 per cent of cases the arterial branch of the superior cerebellar artery "in some way affected the nerve." He discussed why a contiguous artery should produce pain in the trigeminal nerve and should not produce disturbances in other nerves. Dandy further claimed that increasing age, arteriosclerosis and frequently associated hypertension cause elongation of the basilar artery, which becomes S-shaped, and the bulge of the "S" reaches the trigeminal nerve. Schaeffer[3] and de Schweinitz,[4] in their

---

Read at a meeting of the Philadelphia Neurological Society, Dec. 17, 1937.

From the John L. Eckel Neuropathologic Laboratory of the University of Pennsylvania Graduate School of Medicine.

1. Pappenheim, M.: Trigeminusneuralgie durch Druck der arteriosklerotisch veränderten Art basillaris auf den Trigeminusstamm, Wien. med. Wchnschr. **76:** 104, 1926.

2. Dandy, W. E.: Concerning the Cause of Trigeminal Neuralgia, Am. J. Surg. **24:**447, 1934.

3. Schaeffer, J. P.: Some Points in the Regional Anatomy of the Optic Pathway, with Especial Reference to Tumors of the Hypophysis Cerebri and Resulting Ocular Changes, Anat. Rec. **28:**243, 1924.

(Footnotes continued on next page)

study of the regional anatomic relations of the optic pathway, with special reference to tumor of the hypophysis cerebri and resulting ocular changes, observed that at times the optic nerves are grooved by the adjacent carotid blood vessels. It is possible for field defects to result from this condition.

The question of aneurysm will not be considered in this paper, but I wish to focus attention on the fact that aneurysmal dilatations may produce the changes that I am describing, but to a more marked degree. In the cases that will be discussed, pressure was exerted by blood vessels which were not aneurysmal. The conditions produced by sclerosis and elongation of the vessel so compressed the brain substance that clinical signs and symptoms of a definite nature were noted.

REPORT OF CASES

CASE 1.—*History.*—G. W., a man aged 50, was admitted to the hospital on Dec. 2, 1936. The history of his illness antedated his admission by four months, when there began dull, boring occipital headache which radiated to the frontal region. The headache had been more or less constant. Twenty-four hours before his admission the patient began to have projectile vomiting. He attributed this to eating candy. Dizziness had also been present for a month or more. He claimed that only in the last four weeks had he had difficulty in walking. It had been noted by others that he staggered, and he stated that he inclined toward the left. There was no increase in the difficulty in walking at night. Shortly after the onset of the headache he noticed that he saw double and that print was becoming blurred.

The patient had had no previous illness since the acute infectious diseases of childhood, except for an attack of vertigo on the street four months before. He had collapsed and been taken to a hospital, where he remained for twenty-four hours. He was told at that time that he had high blood pressure. He gave a definite history of an initial syphilitic lesion fifteen years before. No treatment had been received.

The patient had been married for ten years. There had been no children and no miscarriages.

Physical Examination.—The patient lay in bed on his left side, in no apparent discomfort. He weighed 150 pounds (68 Kg.), which he claimed was his average weight. The blood pressure was 250 systolic and 170 diastolic. The pupils were small and reacted sluggishly to light and in convergence. The extraocular movements were normal. Definite nystagmus was present on lateral movements of the eyeballs, especially to the left. Speech was slurring. There was tremor of the lips in talking. The tongue did not deviate from the median line. There was marked incoordination on the left side in the finger to nose and the heel to knee test. There was no disturbance in coordination of the right side of the body. The reflexes were obtained bilaterally and were equal on the two sides. There was no disturbance of sensation. There was no Babinski sign and no clonus. A Kernig

4. de Schweinitz, G. E.: Concerning Certain Ocular Aspects of Pituitary Body Disorders, Mainly Exclusive of the Usual Central and Peripheral Hemianopic Field Defects, Bowman Lecture for 1923, London, Adlard & Son & West Newman, Ltd., 1924.

sign could not be obtained. The patient inclined to the left in standing and staggered to the left in walking.

Examination of the heart showed no precordial bulging and no thrills. The apex beat was visualized in the sixth interspace in the midclavicular line. The left border was 11 cm. to the left, and the right border 3 cm. to the right, of the midsternal line. The base was in the third interspace. The heart action was tumultuous. The apical sounds were loud, with a presystolic murmur transmitted to the left axilla. The aortic second sound was intensified. An extrasystole was heard at approximately every fifteenth beat. The border of the liver was palpable 2 cm. below the right costal margin and was tender to pressure. The spleen was not palpable. The arteries were firm; the radial pulses were booming, but without a "pistol shot" sound.

The patient was of good intelligence and cooperated well during the examination. There was no aphasia. He was oriented and coherent. He showed neither delusions nor hallucinations.

Diagnosis.—In view of the history and the focal character of the signs, a differential diagnosis of a cerebellar lesion, especially a tumor, arteriosclerosis with hypertension and syphilis had to be made.

Laboratory Data.—The urine had a specific gravity of 1.017 and showed a heavy trace of albumin, with hyaline and granular casts and many leukocytes but no blood. The red blood cells numbered 5,900,000, and the white cells, 15,300; the hemoglobin content was 14.9 Gm. per hundred cubic centimeters of blood. The sugar content of the blood was 157 mg. per hundred cubic centimeters at the first examination, with 18 mg. of urea; later the sugar concentration of the blood became 169 mg., and the urea content, 10 mg. The Wassermann reactions of the blood and spinal fluid were negative with all antigens. The cell count of the spinal fluid was 14 per cubic millimeter, but many red cells were present; there was a faint trace of albumin, and the colloidal gold curve was 2333221100. A roentgenogram of the skull showed nothing abnormal.

Ocular and Vestibular Examination.—There was blurring of the margins of the disks, with dilatation of the veins and wide areas of exudation along the venous margins. A Bárány test for cerebellar lesion gave normal results.

Course.—While the patient was in the hospital the vertigo persisted. Headache became less severe. He did not vomit when lying on the left side. In view of the possibility of a cerebellar tumor, a spinal puncture was not made until five days after admission. At that time the spinal fluid pressure was 50 mm. of mercury; 20 cc. of fluid was carefully removed, with a final reading of 12 mm. Gradually the cerebellar signs became progressively more severe. The blood pressure did not decrease even with rest in bed, but, on the contrary, the diastolic pressure rose to 186 mm. During the night of December 24 the patient died suddenly.

Pathologic Examination.—Autopsy showed all the evidences of chronic cardiovascular-renal disease, with dilatation of the heart, granular kidneys and severe atherosclerosis of nonsyphilitic type. Gross study of the brain showed sclerotic, tortuous blood vessels, but with no gross lesions of the cerebrum. Within the cerebellum were two recent hemorrhages. The clinical picture of the focal lesion involving the cerebellar pathways was amply explained by erosion of the left lateral portion of the medulla by an enlarged tortuous, sclerotic vertebral artery (fig. 1).

The clinical picture was confusing. The patient admitted having had an initial syphilitic lesion fifteen years prior to onset of the condition.

He had never received treatment. Syphilis, therefore, had to be considered as the first possibility, despite the negative serologic reactions.

The second possibility was severe hypertension. All the clinical features, even the evidences of a focal lesion producing cerebellar signs, could have been attributed to this condition alone. Softening might have occurred in the course of hypertension and arteriosclerosis to account for the clinical manifestations. The fact that the intracranial pressure was extremely high would not have militated against this diagnosis. It is known that in cases of vascular hypertension increased intracranial pressure may be one of the manifestations.

The third possibility, in view of the progressive nature and course of the focal manifestations, was that of a slow-growing lesion. While the patient was in the hospital the focal symptoms increased, so that many

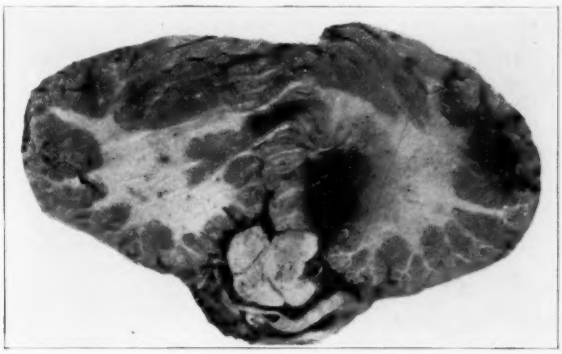


Fig. 1.—Erosion of the lateral portion of the medulla by an enlarged and sclerotic vertebral artery.

clinicians who studied him expressed the belief that the case was one of arteriosclerosis and hypertension, together with a small expansile lesion in the posterior fossa.

Autopsy disclosed a severe degree of atherosclerosis throughout the body. This accounted for the general signs and symptoms that were present. The focal manifestations, however, were found to be the result of gradual pressure and erosion against the left lateral surface of the medulla by a sclerotic blood vessel. This acted as a small tumor, and the pulsations during life must have been instrumental in gradually eroding the soft tissue of the medulla. The vessel was dilated and tortuous, but was not aneurysmal. It is well known that pulsating blood vessels, even though they are not dilated, may erode bone. Under abnormal conditions, such as when the vessel is aneurysmal, erosion of bone, as shown in the roentgenogram, may be one of the diagnostic signs. It is not difficult to visualize the pressure and erosion that may

occur as the result of pulsation against the soft parenchymatous structure of tortuous, sclerotic blood vessels, even though not aneurysmal.

Cases of a similar sort, in which parenchymatous tissue was compressed and eroded by sclerotic blood vessels, have not found their way into the literature. A case such as is reported here is extremely rare.

It is true that only in certain parts of the central nervous system is it possible to produce from a small erosion involvement of structures of such importance. Pressure against other parts of the brain stem is not uncommon and may cause no recognizable clinical picture. This is exemplified by a recent case in which erosion was produced by vascular compression against the anterior surface of the pons. In this case there were no clinical signs or symptoms, and a diagnosis could not have been made during life.

CASE 2.—M. L., a white man aged 70, was admitted to the hospital on Feb. 7, 1935. He complained that he suffered from convulsions and loss of memory. It was stated that for ten years the patient had had convulsive seizures of grand mal type. They were irregular in occurrence, but averaged about one a month. In addition to these major attacks, there were occasional petit mal spells. The family had noticed that for the past five years the patient had showed lapses of memory, particularly for recent events. There was no history of a similar disturbance in the family.

Physical Examination.—The patient appeared older than the given age of 70. There were no neurologic evidences of gross lesion of the central nervous system. Urinalysis showed a large amount of albumin, absence of sugar and numerous granular casts.

Course.—While the patient was under observation, pneumonia developed. He died one week after admission.

Pathologic Examination.—Gross examination of the brain revealed tortuous, sclerotic blood vessels. The brain was small, and there was considerable atrophy of the convolutions. The membranes were thickened but not edematous. Frontal section through the brain showed slight dilatation of the ventricular system. The cortex was somewhat narrowed. Despite careful search for areas of softening, none was seen. The spinal cord was not examined.

Microscopic examination showed hyperplastic meninges, containing débris within large macrophages. There was a reactive process in the subarachnoid space, as shown by the occasional presence of perivascular infiltration around some of the veins. The blood vessels within the meninges were sclerotic. The vessels of larger caliber showed atheroma, while those of medium size had thickened and hyalinized walls. The smaller blood vessels were prominent because of swelling and proliferation of the lining cells. Many of the large vessels over the cortex grooved the surface of the brain in such a way as to form nests for themselves (fig. 2). Many were bound down by fibrous tissue so that they were not free within the subarachnoid space, but lay directly on the cortex and, for that reason, had produced the grooving. The areas in which the vessels grooved the cortex were irregularly scattered.

In the cortex there was lessening in the number of ganglion cells, but no actual areas of complete cell loss. Even in the cornu ammonis, the area known as Sommer's sector was relatively intact. Some of the larger blood vessels within

the sylvian fissure in relation to the cornu ammonis particularly were bound down and had grooved the brain. In the region of the brain stem sclerotic blood vessels of the same type occurred, but at no point were they encased in a connective tissue network. For the most part they lay free within the subarachnoid space.

The clinical picture was that of convulsive seizures beginning at the age of 61. The seizures differed in no way from convulsions arising

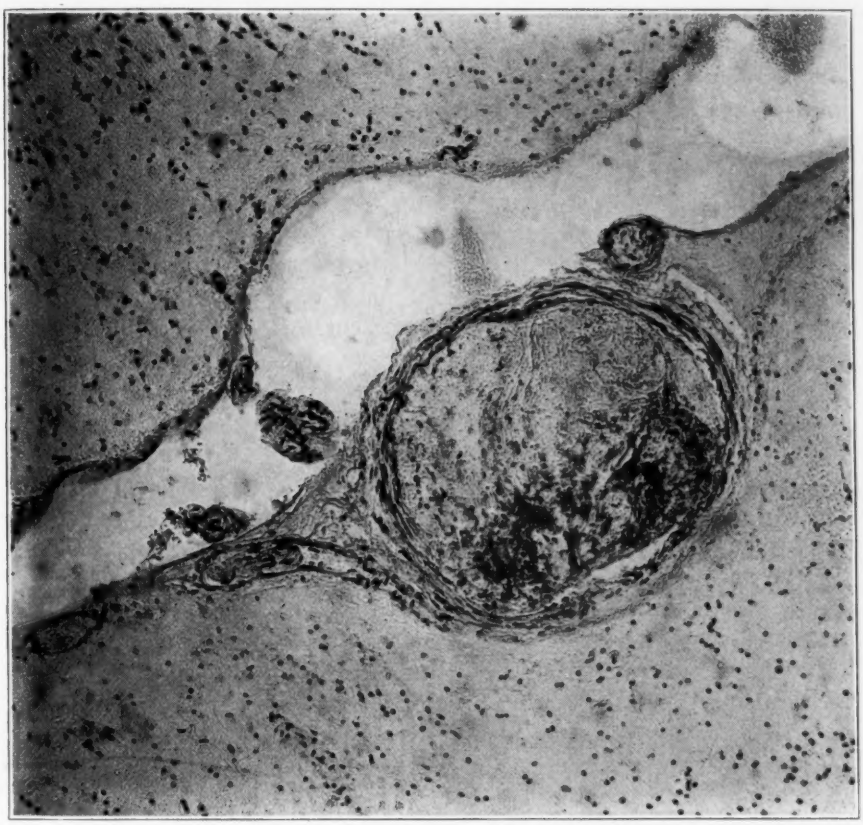


Fig. 2.—Erosion of the cortex by a blood vessel.

from other etiologic agents. Aside from loss of memory for recent events the patient showed no evidence of gross organic disturbance of the central nervous system. At autopsy the outstanding feature of the brain was not the presence of markedly sclerotic blood vessels but the fact that many of them were actually embedded in the brain tissue and grooved the substance of the brain. Many were so bound down that they could not expand at the expense of the subarachnoid space, as usually happens in arteriosclerosis.

It is not difficult to visualize what happened during life in a condition of this sort. It is easy to see how a pulsating mass of blood vessels attached to the cortex would exert pulsating pressure on the brain substance with every systole of the heart. This may not be the true explanation for the convulsive seizures in this case. It is true, however, that it is a factor which has been overlooked in consideration of the etiologic basis of convulsions which occur in the aged. It may be argued that some pressure is exerted on the brain in every case of arteriosclerosis. This is the sort of question that Dandy [2] attempted to answer in his discussion as to why in certain cases pressure by a blood vessel produces pain in the face and why in other cases pain is absent. Dandy's explanation was interesting. He cited the problem of gallstones with and without accompanying pain. He stated that when a patient with gallstones has pain "the gallstones are unquestionably the cause" and yet in many cases gallstones are present without pain. He claimed that in the same way lesions may attack the sensory root of the fifth nerve in the angle without the actual production of pain. Two additional factors may be considered in answer to the question I have propounded: One is the variation in the convulsive threshold in different cases; the other is the fact that certain areas of the brain may be more likely to produce convulsive attacks if they are irritated. This will be discussed at greater length in the general consideration of the problem.

Against the aforementioned facts may be argued the point that the pulsation of the blood vessels continues day and night; if the convulsive attacks were the result of this pulsation, status epilepticus should be the result. This argument can be answered by stating that when a small tumor somewhere in the brain produces convulsive attacks these attacks occur at irregular intervals and are not continuous. There must be summation of stimuli up to a certain point; when that threshold is reached the convulsive attacks occur.

Special mention was made of the fact that in the present cases Sommer's sector was normal. A great deal of stress has been laid by the Spielmeyer School on the histopathologic changes in this part of the central nervous system in association with epilepsy. Cases have been described in which no change was seen in Sommer's sector, even though the patient had convulsive attacks for years preceding death. The condition in my case, therefore, while an exception to the rule, is not unknown.

The question of the mechanism of the change in Sommer's sector may be referred to at this point, in view of the fact that Uchimura,[5] in Spielmeyer's laboratory, observed only a single long blood vessel supplying that area of the brain. The question arises whether the lesion

5. Uchimura, J.: Ueber die Gefässversorgung des Ammonhornes, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:1, 1928.

in Sommer's sector is the cause or the result of the epileptic attacks. The mechanism of a convulsive attack is not yet known. It is recognized that many factors may produce convulsions. Convulsive attacks during the senium are not common. Any factor which may be responsible for the attack should be carefully investigated and recorded. The blood vessels should receive careful study. Eventually, some solution to the problem may be found.

COMMENT

The production of neurologic signs and symptoms from pressure by a sclerotic and tortuous blood vessel is not unknown. The gross changes that have thus far been described in the literature have been related to the fifth cranial nerve, with trigeminal neuralgia as the clinical picture. Dandy,[2] in particular, has stressed this etiologic factor in the development of trigeminal neuralgia in some cases which he has had occasion to observe at operation. Dandy observed that the artery pressed on the nerve in 30.7 per cent of a series of 215 cases and expressed the belief that the pain was the result of pressure on the sensory root.

In the first of the 2 cases described in this paper, there were clinical evidences of a focal lesion of the brain stem. The general symptoms can easily be explained on the basis of increased intracranial pressure secondary to vascular hypertension. The focal symptoms, however, were not so easily accounted for. The clinical picture as a whole resembled a growing lesion of the brain. At the time of the patient's death no final diagnosis could be made. It was thought that a vascular lesion could be excluded by the progressive nature of the lesion. Pressure against the medulla by a tortuous and sclerotic vessel did not even come into consideration.

In the second case reported the clinical picture was mainly that of convulsive seizures in the senium. There was nothing in the brain itself to account for the condition. It is known that convulsive seizures can occur from irritative lesions in the brain. All have had experience in encountering gross lesions in cases that were thought to be those of idiopathic type. In many of the cases in which the diagnosis was made and the lesion was accessible to surgical treatment, the convulsions completely disappeared after removal of the offending factor. It thus becomes evident from cases of this sort that continued irritation of the brain from even comparatively small growing lesions may occasion generalized convulsive seizures. It is true that irritation of certain parts of the brain will produce convulsive attacks more readily than that of other portions. Reference should be made to Parker's [6] investigations on this problem at the Mayo Clinic. He showed that tumors in certain

6. Parker, H. L.: Epileptiform Convulsions: The Incidence of Attacks in Cases of Intracranial Tumor, Arch. Neurol. & Psychiat. **23**:1032 (May) 1930.

parts of the brain are more likely to produce convulsive attacks than in others. He found that in 21.6 per cent of 313 cases of tumor major epileptic seizures occurred. In all cases the tumor was situated above the tentorium. In most of the cases in which convulsions occurred the tumor was situated in the frontal, parietal or temporal lobe of the brain, in descending order of frequency. It is thus possible that the low incidence of convulsive attacks in older persons may at least be partly explained by the fact that only a small percentage have compression of susceptible parts of the brain. The other factors that may be responsible need not be discussed.

That irritation of the brain can result from continuous pounding against it by sclerotic blood vessels is not difficult to visualize. One can picture that a pulsation taking place with every beat of the heart from 70 to 100 a minute, would eventually wear a groove in the brain. Some clinical effect from a condition of this sort must occur, particularly if the pounding is in certain parts of the brain and in susceptible persons. The susceptibility of the patient needs comment. Pike [7] and his associates, at Columbia University, showed that the convulsive threshold is lowered under certain conditions. They found that a much smaller dose of a convulsant agent, e. g., absinth, is necessary to produce convulsive seizures in animals in which they had traumatized the head some time previously. It is possible that such an explanation may be invoked in certain cases in which convulsive seizures occur with less provocation than they do in others. It may thus be possible that in a small number of patients trauma to the head many years before may be one of the factors predisposing to convulsive seizures.

The effect of irritation from a small lesion is illustrated by a recent case in which a woman had had convulsions for twelve years preceding death. They began at the age of 16 years. A diagnosis of idiopathic epilepsy had been made. She died of pneumonia. At autopsy a tumor, 2 cm. in diameter, which filled the inferior horn of the ventricle on the left side was observed. The tumor had grown from the choroid plexus. It was a slow-growing tumor and probably had been present during the entire period of the convulsive history. A case of this sort illustrates how mild irritation, if in the proper location, may produce convulsive attacks.

SUMMARY AND CONCLUSIONS

1. The effect of slow compression of the parenchyma of the medulla by a sclerotic blood vessel is illustrated by a clinicopathologic report of a case in which general and focal signs and symptoms suggestive of

7. Pike, F. H.; Elsberg, C. A.; McCulloch, W. S., and Chappell, M. N.: The Problem of Localization in Experimentally Induced Convulsions, Arch. Neurol. & Psychiat. **23**:847 (May) 1930.

a tumor of the brain were present. The former signs and symptoms were explained by the occurrence of vascular hypertension and consequent increased intracranial pressure. The focal signs were observed to be due to slow erosion of the lateral portion of the medulla by a sclerotic and tortuous blood vessel, which acted in the nature of a small expanding neoplasm.

2. A case of convulsive seizures in an aged man was studied clinically and pathologically. Observations at autopsy showed erosion of the brain by sclerotic and frequently tortuous blood vessels, which were bound down to the cortex. Aside from this lesion the case did not differ from other cases of arteriosclerosis occurring in older persons.

3. An effort was made to correlate the anatomic observations in case 2 with the clinical picture. Suggestion was made that the continued irritation of the pulsating blood vessels against the brain substance may have been responsible, in part at least, for the convulsive attacks. An analogy was drawn between the irritation that may result from a neoplasm and that from the pulsation of the blood vessels themselves.

4. Suggestion was made that when a sclerotic vessel is so bound down that it is unable to expand at the expense of the subarachnoid space the brain may be irritated to the point of producing convulsions in susceptible persons. As a rule sclerotic and dilated blood vessels expand chiefly at the expense of the subarachnoid space.

5. The cases described in this paper correspond with those, already reported in the literature, in which pressure against the trigeminal nerve by an adjacent blood vessel was held responsible for the symptom complex of trigeminal neuralgia. Dandy,[2] in his well illustrated article, attributed the pain in 30.7 per cent of his cases in which operation was performed to this one cause.

DISCUSSION

DR. F. C. GRANT: I was interested in Dr. Winkelman's reference to Dandy's observation with regard to pressure of a vessel against the trigeminal nerve as a possible cause of major trigeminal neuralgia. It seems curious that if a vessel presses against a nerve the pain is not much more continuous than that in major trigeminal neuralgia, in which remission is part of the disease. After Dandy made his suggestion, my colleagues and I took occasion to examine the brain in 12 cases in which there was no history of major trigeminal neuralgia; in 3, at the time of autopsy, a vessel was observed to be in relation to the trigeminal nerve. While this does not have any particular bearing on Dr. Winkelman's paper, it suggests that the etiologic factor of pressure in major trigeminal neuralgia needs further demonstration or proof. There must be many more cases in which anomalous vessels press against the trigeminal nerve and do not cause pain. We have had 3 cases in which there was no such effect.

DR. N. W. WINKELMAN: Dr. Grant's points are well taken. Dandy himself tried to forestall the question that Dr. Grant has raised this evening by answering it in his article. I mentioned Dandy's observations because I could find little or nothing else in the literature which had a bearing on the problem I was discussing. I am unable to answer the question whether the proximity of the blood vessel to the fifth cranial nerve was a factor in the production of pain in some of the cases in which Dandy performed operation.

CEREBRAL CIRCULATION

I. REACTION OF PIAL ARTERIES TO EPINEPHRINE BY DIRECT APPLICATION AND BY INTRAVENOUS INJECTION

MOGENS FOG, M.D.
COPENHAGEN, DENMARK

Since the general biologic action of epinephrine became known, numerous investigations have been carried out in order to determine its influence on the cerebral blood vessels. This interest is probably due to the conception, first advanced by Brodie,[1] that in any given vascular area a definite response to epinephrine is an expression of sympathetic vasomotor innervation. Conversely, the lack of constrictor response to epinephrine provides evidence that the sympathetic system has no influence on the arteries of the organ in question. Recent investigation of the mode of transmission of sympathetic nerve impulses to organs supports this point of view.

The effect of epinephrine on the cerebral blood vessels has been studied chiefly by four experimental methods: (1) intravascular injection into a living animal; (2) injection into the circulation of an isolated surviving head; (3) immersion of excised arteries in solutions of epinephrine, and (4) irrigation of the surface of the brain (outside the arachnoid membrane) of a living animal.

The present paper is divided into two parts: The first deals with the local application of epinephrine to the surface of the brain; the second, with intravenous injection.

LOCAL APPLICATION OF SOLUTIONS OF EPINEPHRINE TO THE SURFACE OF THE BRAIN

In the past, investigators have obtained conflicting results. Biedl and Reiner [2] observed constriction of the pial vessels through a trephine opening and also noted reduction in outflow from the cerebral veins when a solution of epinephrine was dripped on the surface of the brain. Forbes and Wolff [3] observed constriction of the pial arteries, with no

---

From the Medicophysiologic Institute of the University of Copenhagen.

This investigation was aided by a grant from the Rockefeller Foundation.

1. Brodie, T. G.: J. Physiol. **30**:476, 1904.

2. Biedl, A., and Reiner, M.: Arch. f. d. ges. Physiol. **79**:158, 1900.

3. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

accompanying change in systemic blood pressure, when the arachnoid beneath a cranial window was irrigated with a solution of epinephrine.

Later, Forbes, Finley and Nason [4] showed that pial arteries of less than 50 microns in diameter appeared to change little, if at all, in contrast to the distinct narrowing of the larger arteries, when epinephrine was applied.

Florey [5] applied a solution of epinephrine hydrochloride (concentration, from 1:1,000 to 1:10,000) to the surface of the brain and failed to see constriction in any instance. On the other hand, neither Howe and McKinley [6] nor Riser, Mériel and Planques [7] observed any pronounced constriction. Ley and de la Fontaine-Verwey [8] also noted none under normal conditions, but after an intravenous injection of sodium hydroxide the local application of epinephrine constricted the pial arteries strongly.

In view of these conflicting results, it seemed desirable to reexamine the subject, using a method which would exclude, so far as possible, errors arising from mechanical or thermal irritation of the cerebral vessels. Florey [5] had shown their sensitiveness to such influences.

Method.—Cats were anesthetized with a mixture of chloral and dextrose (chloralose), from 3 to 3.5 cc. per kilogram of body weight, or butyl-beta-bromallylmalonylurea (pernoston), 0.6 cc. per kilogram. The pial arteries were observed directly through a cranial window according to Forbes's technic, a Leitz Ultropak microscope (magnification, × 110) being used. The blood pressure, the pulmonary ventilation and the diameter of the arteries were recorded synchronously on the rotating cylinder of a kymograph (compare Fog [9]). The arachnoid beneath the cranial window was irrigated alternately with a solution of epinephrine and Ringer's solution, under a constant pressure of from 100 to 200 mm. of water and at a temperature of from 35 to 37 C., by means of an apparatus shown in figure 1. Two bottles, containing a solution of epinephrine hydrochloride and Ringer's solution, respectively, were placed at the same height (from 25 to 30 cm.) above the animal's head. The liquids were led through separate spiral tubes, placed in a water bath, to a two way cock, which was connected with the cannula of the window by a single tube. A side opening on each of the tubes (not shown in the figure) just above the cock permitted emptying of the cooled liquid in the tubes previous to the start of the experiment. The other cannula of the window

4. Forbes, H. S.; Finley, K. H., and Nason, G. I.: Cerebral Circulation: Action of Epinephrine on Pial Vessels, Arch. Neurol. & Psychiat. **30**:957 (Nov.) 1933.

5. Florey, H.: Brain **48**:43, 1925.

6. Howe, H. S., and McKinley, E.: Cerebral Circulation, Arch. Neurol. & Psychiat. **18**:81 (July) 1927.

7. Riser, M.; Mériel, P., and Planques: Encéphale **26**:501, 1931.

8. Ley, J., and de la Fontaine-Verwey, B. C.: Compt. rend. Soc. de biol. **101**:478, 1929.

9. Fog, M.: Om piaarteriernes vasomotoriske reactioner, Danish Dissert., 1934.

was connected with a rubber tube, from which the solution could flow into a measuring glass after passing the pia.

During the experiment Ringer's solution was first allowed to flow for at least eight or ten minutes after constant conditions with regard to diameter of the pial arteries, arterial and intracranial pressure and temperature had been established. Thereafter, by turning the cock, a solution of epinephrine was allowed to flow for periods varying from seven to twenty-six minutes. In several experiments the effect of epinephrine was tested again after intermittent perfusion with Ringer's solution. In one cat the cerebrospinal pressure was controlled through a cannula in the cisterna magna and was found to be constant during the various irrigations.

The solution of epinephrine hydrochloride was made by dilution of a 1 : 1,000 concentration with Ringer's solution. The dilutions were freshly pre-

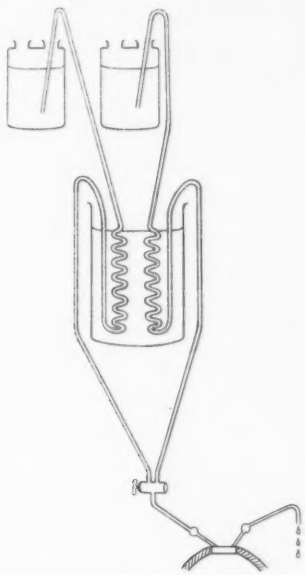


Fig. 1.—Apparatus for irrigation beneath the cranial window.

pared for each experiment, and care was taken to see that the Ringer solution used for irrigation as control and the solution of epinephrine had the same p_H. The hydrogen ion concentrations proved to be 7.08 and 7.09, respectively.

Experiments.—The experiments fall into two groups according to the size of the pial vessels which were examined: (a) those in which the arteries were less than 50 microns, and (b) those in which the arteries were more than 100 microns in diameter.

(*a*) In this group the arterial diameters ranged from 20 to 40 microns. In 5 cats irrigations were made six times with a solution of epinephrine hydrochloride of 1 : 100,000 concentration and six times with a solution of 1 : 10,000 concentration. Fourteen irrigations with Ringer's solution were carried out as controls.

The quantity of fluid used in irrigation per minute varied from 1 to 7 cc. The amount was kept uniform for both the Ringer and the epinephrine solution in any given animal.

The results showed no measurable change in the diameter of the small arteries of this group, even during long-continued exposure to epinephrine (fig. 2).

Often, a slight rise in blood pressure was seen, indicating absorption of the active epinephrine component. When a solution with a concentration of 1:10,000 was used, this elevation in pressure was seen in every case. The maximum rise was 30 mm. of mercury.

In 1 experiment an old, discolored solution of epinephrine was used. The arteriole under observation dilated from 29 to 42 microns. It constricted again to its original size after subsequent irrigation with Ringer's solution for eight minutes. A new dilation was obtained on repeating the experiment. When fresh solutions were used dilator effects were never observed.

(*b*) In 6 cats, arteries of a diameter of from 100 to 270 microns were observed during eight irrigations of epinephrine hydrochloride, in a concentration of 1:100,000. As in the first series, Ringer's solution was used as a control in

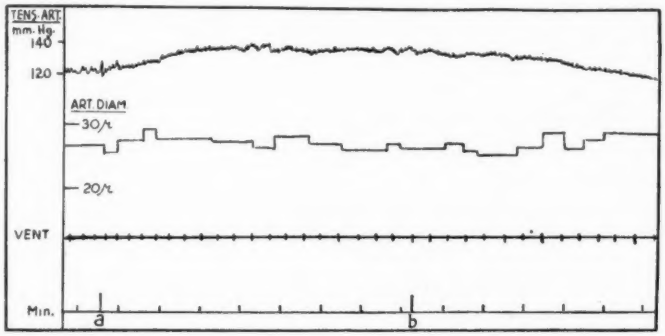


Fig. 2.—In the graph, *a* to *b* indicates application of a solution of epinephrine hydrochloride (concentration, 1:10,000) directly to the pia for seven and a half minutes. There was no reaction of the arteriole.

every instance. In this group the arteries invariably constricted, the diminution in diameter ranging from 3 to 30 per cent (fig. 3). The larger arteries showed the most pronounced constriction. No significant alterations in the systemic blood pressure occurred, and the pulmonary ventilation remained constant throughout the experiments.

The results of these experiments confirm previous observations [4] that the pial arteries present different reactions to local application of epinephrine, according to their size. The smaller vessels do not constrict, whereas the larger arteries (of more than 100 microns diameter) invariably constrict. This constriction, however, is slight when compared with that seen in other vascular areas of the body.

The conflicting results which have been obtained in the past may be explained partly by differences in the size of the arteries on which

experiments were made and partly by failure to recognize the sensitiveness of these vessels to direct irritation, thermal and mechanical. An artery which is already dilated by trauma or other cause may show a different response to epinephrine from that which it would have shown before such dilation. Moreover, it has been found that the diameter of pial arteries is strongly affected by intravascular pressure through alterations in the tonus of the walls.[10] Therefore the size of an artery at any given time (and its possible divergence from the normal) can be appreciated only when the actual level as well as the behavior of the arterial pressure is known. Finally, it appears from my own observa-

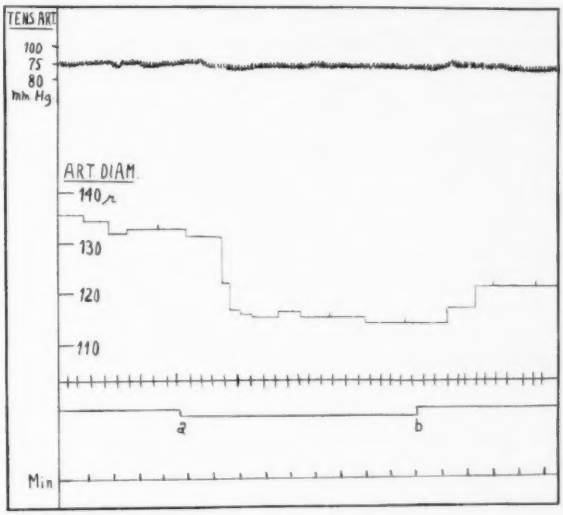


Fig. 3.—In the graph, *a* to *b* indicates application of a solution of epinephrine hydrochloride (concentration, 1:100,000) directly to the pia, with reaction of a large artery.

tions that prolonged irrigation of the surface of the brain with solutions of epinephrine in concentrations exceeding 1:100,000 will cause a rise in systemic blood pressure. This rise in pressure may, in turn, affect the caliber of the pial vessels by wholly indirect means, i. e., through action on the walls of the vessels not by the epinephrine itself but by the change in intravascular pressure.

10. Forbes, H. S.; Nason, G. I., and Wortman, R. C.: Cerebral Circulation: Vasodilation in Pia Following Stimulation of Vagus, Aortic and Carotid Sinus Nerves, Arch. Neurol. & Psychiat. **37**:334 (Feb.) 1937. Fog, M.: Cerebral Circulation: Reaction of Pial Arteries to Fall in Blood Pressure, ibid. **37**:351 (Feb.) 1937.

INTRAVENOUS INJECTION OF EPINEPHRINE

The literature on this subject has been referred to by Finesinger and Putnam [11] and Bouckaert and Jourdan,[12] so that it seems unnecessary to review it here. Suffice it to say that the results of experimentation in this field have been as conflicting as those which have been described in the preceding section.

In attacking this problem it seemed to me essential to employ a method which permits clear differentiation between the chemical action of epinephrine and the indirect effects caused by a rise of blood pressure. The reason is that I have found that a rise of blood pressure, no matter how caused, will bring about constriction of the pial arteries.[13]

Method.—The reactions of pial arteries were observed and recorded, as described in the preceding section. The blood pressure (common carotid artery) was recorded by a membrane manometer, after the principle of Trendelenburg. Most of the 20 cats experimented on were subjected to artificial respiration. Butyl-beta-bromallylmalonylurea was used for anesthesia. Epinephrine hydrochloride, in a concentration of 1 : 100,000, was injected by syringe or instilled from a buret into the external jugular vein.

A T-cannula was inserted into the abdominal aorta below the origin of the renal arteries and connected to a blood pressure–compensating apparatus, as shown in figure 4. A wide glass tube (*B*) (volume, 200 cc.), partly containing defibrinated blood, was connected above to a T tube, one arm of which led from an oxygen tank. The other arm was continued to a vertical tube (*A*) which opened under mercury in a container, 40 cm. in height. This tube could be lowered or raised to any level under the surface of the mercury. During the experiments oxygen was continuously led from the tank under excess pressure, so that it bubbled out under the mercury. Therefore the pressure exerted on the surface of the blood in the wide tube (and thereby transmitted into the circulatory system of the animal) was determined by the height of mercury over the opening of the vertical oxygen tube (*a*).

When epinephrine was injected into the jugular vein the blood rose within the receptacle to a maximum level and then gradually fell again as the action of the substance decreased. Meanwhile, the systemic blood pressure remained constant. By means of a stopcock, the apparatus could be excluded. In this way, it was possible to compare the effect of epinephrine on the pial vessels during periods of "compensated" and of "uncompensated" blood pressure. Furthermore, elevations of blood pressure to a similar height and for the same duration as those produced by uncompensated injection of epinephrine could be produced by temporarily increasing the height of mercury over the opening of the oxygen tube (*a*). In these cases the defibrinated blood ran into the vessels of the animal, and the rise in pressure was caused by an increase in the volume of circulating

11. Finesinger, J., and Putnam, T. J.: Cerebral Circulation: XXIII. Induced Variations in Volume Flow Through the Brain Perfused at Constant Pressure, Arch. Neurol. & Psychiat. **30**:775 (Oct.) 1933.

12. Bouckaert, J. J., and Jourdan, F.: Arch. internat. de pharmacodyn. et de thérap. **54**:109, 1936.

13. Fog, M.: Cerebral Circulation: II. Reaction of Pial Arteries to Increase in Blood Pressure, Arch. Neurol. & Psychiat., to be published.

blood. Such rises in blood pressure will be referred to in the following sections as "mechanically induced."

Experiments.—Fifty-one intravenous injections of epinephrine hydrochloride were given to 20 cats; in most experiments a dose of 50 micrograms (5 cc. of a concentration of 1 : 100,000) was given in the course of from three to six minutes. The reaction of the arteries to a rise in blood pressure was found to be pronounced when the initial level was low; therefore the arterial tension before injections was kept usually between 70 and 90 mm. of mercury.

In 13 cats, during injection of epinephrine a rise in blood pressure was successfully prevented, so that it was possible to observe the vasomotor responses to the purely chemical action of the substance. When the blood pressure remained constant, arteries of a diameter of less than 50 microns did not constrict (14 injections), whereas arteries of from 100 to 200 microns constricted. The constric-

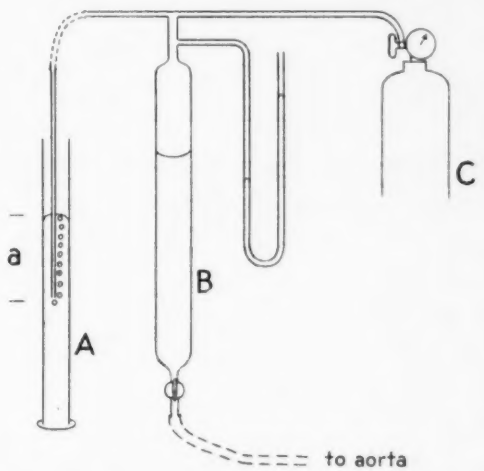


Fig. 4.—Blood pressure–compensating apparatus. *A* indicates the mercury container; *B*, the blood container, and *C*, the oxygen tank.

tions (5 experiments) varied from 4 to 8 per cent of the original size (fig. 5 *A* and *B*).

In experiments on the same animals serving as controls, injections of similar doses of epinephrine were repeated after the blood pressure–compensating apparatus had been excluded by turning the stopcock. The arterial pressure then rose freely. In 22 of 29 experiments the small arteries under these conditions constricted distinctly, while the larger arteries (in 3 experiments) tended to dilate. Twice the arterioles did not react at all. In both these cases there was only a slight rise in blood pressure (less than 12 mm. of mercury). In 5 experiments the arterioles dilated. This occurred three times in 1 cat, which was in an unusually deep state of anesthesia; with rises in blood pressure produced mechanically, also, the arteries of this cat reacted "passively," i. e., by dilatation. In the remaining 2 cases, dilation followed administration of an old, discolored solution of epinephrine. The same solution also caused dilation of the larger pial arteries even when the blood pressure was compensated for. Fresh solutions elicited the usual reactions.

In 7 cats the rise in blood pressure during the injections was not entirely prevented. A small rise occurred while the blood was flowing into the receptacle. When, however, the compensating apparatus was excluded the same dose of epinephrine caused a far greater rise of blood pressure. It was evident that the reactions of the small arteries were dependent primarily on the rise in blood pressure alone.

Further experiments supported this conclusion. With several cats, various irregular and atypical reactions followed the injection of epinephrine, involving

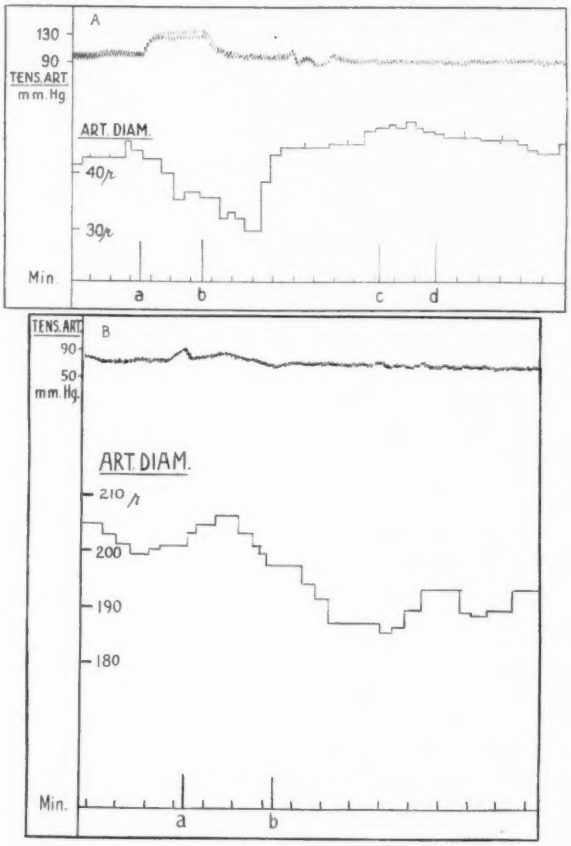


Fig. 5.—*A*, reaction of a small pial artery (arteriole) during intravenous injection of epinephrine, (*a* to *b*) without compensation for the rise in blood pressure and (*c* to *d*) with compensation for the blood pressure.

In *B*, *a* to *b* indicates the reaction of a large artery during injection of epinephrine, when compensating for the blood pressure.

both the blood pressure and the pial arteries. When the blood pressure was raised to the same extent by mechanical means in these cases, the pial arteries responded just as they had to the injections of epinephrine. Figure 6 *A* and *B* is representative of 2 such experiments. Perhaps the arterial lumen returned to its

original size somewhat more slowly after administration of epinephrine, but the difference was not marked.

In a number of cases the volume of blood which flowed into the receptacle during the course of a compensated injection of epinephrine was measured. For 50 micrograms of epinephrine hydrochloride (given within from three to six minutes) the outflow averaged 20 cc. Individual variations, however, were large (from 3 to 60 cc.). The animals showing the most lively vascular reactions

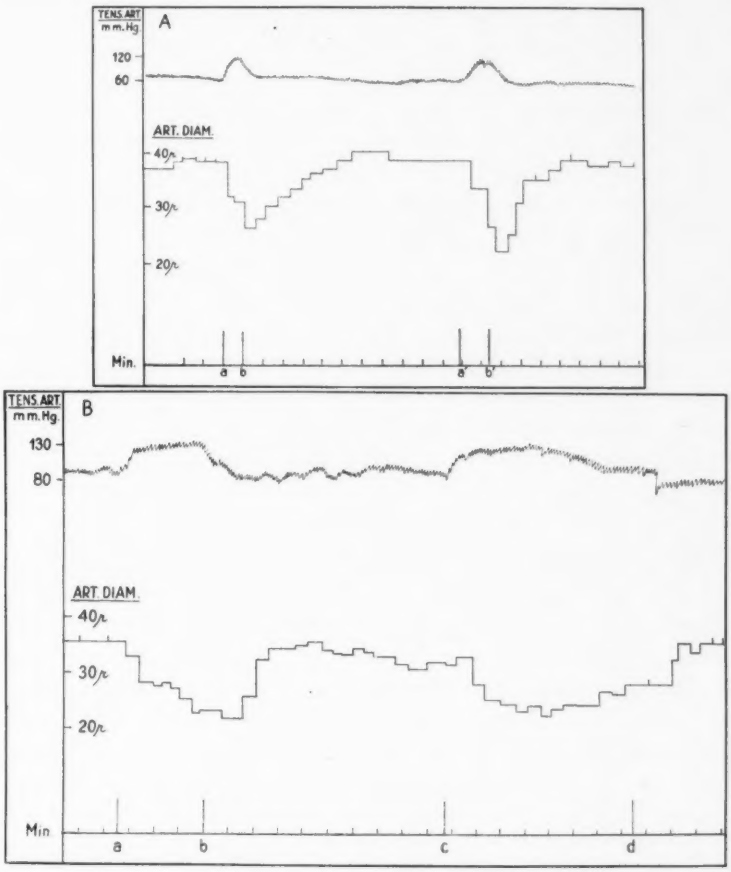


Fig. 6.—*A*, reaction of a pial arteriole during injection of epinephrine of short duration (*a* to *b*), as compared with the reaction to a rise in blood pressure (*a'* to *b'*) produced by the compensating apparatus ("mechanically induced rise").

B, reaction of a pial arteriole during injection of epinephrine of long duration (*a* to *b*), as compared with the reaction during a mechanically induced rise of the same duration (*c* to *d*).

during a rise in blood pressure produced by epinephrine appeared to discharge the largest volume of blood into the receptacle when the compensating apparatus was used. The number of experiments, however, was too few to be certain of this.

The results of these experiments all seem to confirm those which were obtained by the local application of epinephrine. It appears that the direct chemical effect of epinephrine on the pial vessels (as distinct from its indirect effect through modification of the blood pressure) is to cause slight constriction of the larger arteries, but no change in caliber of the arterioles. The latter vessels, however, react by constriction to a rise in blood pressure. My recent experiments have shown that a rise in blood pressure causes constriction of the larger arteries also.[13] This may be preceded by temporary dilatation of a "passive" nature, i. e., mechanical distention.

The feeble response of even the larger pial arteries to epinephrine indicates poor sympathetic innervation of these vessels. This is confirmed by the slight degree of vasoconstriction brought about by electrical stimulation of the cervical portion of the sympathetic trunk.[4] The arterioles apparently have no sympathetic innervation, for they give no measurable response either to epinephrine or to sympathetic stimulation.[9]

In contrast to the partial or total lack of vasomotor control shown by the large and the small arteries, respectively, special sensitiveness seems to be demonstrated by both groups of vessels toward alterations in intravascular pressure. Since the caliber of the small arterioles must be regarded as the most important factor in determining the resistance offered by the vascular bed, their reactions deserve special interest.

SUMMARY

1. When epinephrine is applied locally to the surface of the brain, with care to avoid thermal or mechanical irritation of the walls of the vessels, the larger arteries of the pia constrict slightly, but the arterioles show no change in caliber.

2. When epinephrine is given intravenously and the arterial pressure is kept constant by artificial means, the same vascular reactions occur.

These facts indicate that the sympathetic vasoconstrictor innervation of the pia in the parietal region not only is feeble but is confined to the larger vessels.

A definite rise in blood pressure from epinephrine or other cause, on the other hand, will constrict both the large and the small vessels, the larger arteries usually showing brief preliminary dilatation if the rise is sudden and great. This reaction is "passive" in character, i. e., a mechanical expansion of the walls of the vessels.

Since the caliber of the small arterioles appears to be the main factor in determining the resistance offered by the vascular bed, the behavior of the vessels in the brain is of exceptional interest.

CONGENITAL MORPHOLOGIC ABNORMALITIES OF THE BRAIN IN A CASE OF ABORTIVE TUBEROUS SCLEROSIS

FUNCTIONAL IMPLICATIONS AND BEARING ON PATHOGENESIS OF SO-CALLED GENUINE EPILEPSY

PAUL I. YAKOVLEV, M.D.
WALTHAM, MASS.

In two previous publications [1] the clinical aspects and the nosologic position of tuberous sclerosis in the group of "congenital ectodermoses" were considered in detail. Van Bogaert,[2] in a study of these congenital ectodermal dysplasias, gave an excellent presentation of the subject, with special reference to familial and hereditary factors. Critchley and Earl [3] made a thorough study of the clinical and the morbid anatomic aspects of tuberous sclerosis and reviewed the literature. In typical cases of tuberous sclerosis the highly characteristic congenital abnormalities of the skin, viz., sebaceous adenoma of the face, "shagreen" patches in the sacrolumbar region, tumors of the nail bed and nevoid tumors of the retina, associated with epilepsy and congenital mental defect, permit one to recognize the condition at a glance during life. Autopsy in such cases never fails to reveal the whitish or yellowish hard nodules (tubera) which may be seen almost anywhere in the cerebral hemispheres and brain stem, but which are distinctly more common in the cortex of the medial wall of the hemispheres (gyrus cinguli, hippocampus) and in the walls of the lateral and third ventricles along the sulcus terminalis (striothalamicus) and the rostral portion of the hypothalamus, where they may accumulate and appear like candle gutterings (fig. 1). If only such typical, i. e., clinically manifest, cases are considered, the condition may appear to be relatively rare. There are other cases, however, in which the external

1. (*a*) Yakovlev, P. I., and Guthrie, R. H.: Congenital Ectodermoses (Neurocutaneous Syndromes) in Epileptic Patients, Arch. Neurol. & Psychiat. **26**:1145 (Dec.) 1931. (*b*) Yakovlev, P. I.: Congenital Ectodermoses (Neoplastic Malformations Affecting with Predilection the Skin, Retina, and Nervous System), in Blumer, G.: The Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1936, vol. 9, chap. 27.

2. van Bogaert, L.: Dysplasies neuro-ectodermiques congénitales, Rev. neurol. **63**:23, 1935.

3. Critchley, M., and Earl, C. J. C.: Tuberose Sclerosis and Allied Conditions, Brain **55**:311, 1932.

(cutaneous, retinal) manifestations may be limited to a few pigmented nevi or a single small patch of "shagreen" skin in the lumbar region; even these symptoms may be absent. The epilepsy, with or without mental deficiency, may be the only clinical manifestation of the congenital abnormality of the nervous system. In such cases the recognition of tuberous sclerosis of the brain during life is practically impossible. Such clinically incomplete, or abortive, cases of tuberous sclerosis are more frequent than is generally believed, the condition being often disclosed unexpectedly at autopsy in cases of chronic epilepsy. In the present article I wish to report such a case, in which the diagnosis of tuberous sclerosis during life appeared to be a remote possibility; yet autopsy revealed discrete, but unmistakable, evidence of this condition. This case gives me occasion to describe the characteristic lesion in tuberous sclerosis and to comment on the functional implications which the

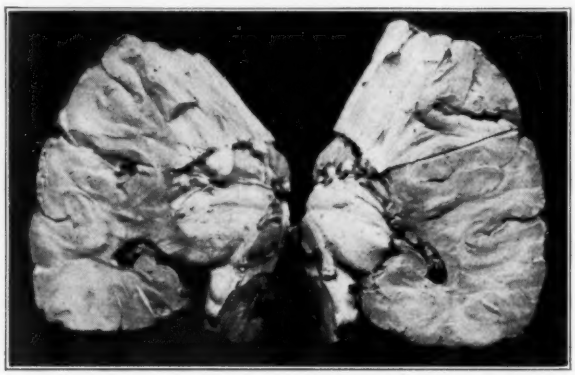


Fig. 1.—The brain in a typical case of tuberous sclerosis, showing multiple ventricular tumors in characteristic location along the striothalamic sulcus bilaterally.

observed morphologic abnormalities may have in relation to the pathogenesis of at least a certain type of "idiopathic" epilepsy, arising on a congenital constitutional background.

REPORT OF A CASE

Clinical History.—B. Q. was admitted to the Monson State Hospital at 13 years of age because of epilepsy and mental deterioration. The family history was without significance except that of the mother's six pregnancies one was ectopic and three ended in miscarriages. A young sister was in good health so far as was known. The patient was born at full term after a normal delivery and during the first years of life was considered normal. At about 7 years of age, when she was in the second grade of grammar school, she began to have epileptic attacks; subsequently, she showed changes in personality associated with impairment of mental faculties.

Menses became established soon after admission to the hospital and were regular and unattended by pain or any discomfort.

On admission, the patient was physically well developed for her age and showed signs of beginning pubescence. However, a psychometric test (Stanford-Binet) revealed arrest of mental development, with an intelligence quotient of 54 and a mental age of 7.2 years, the chronologic age being 13.3 years. General medical examination gave essentially normal results. The Wassermann reaction of the blood was negative. Neurologic examination showed slight weakness of the right arm and leg, with a tendency to an athetoid posture of the right hand, slight exaggeration of the tendon reflexes on the right side and a Babinski sign bilaterally; this was constant on the right side but variable on the left. There were no other neurologic abnormalities. The eyegrounds were normal. Lumbar puncture showed a pressure of 110 mm. of water with Ayer's manometer; there were 2 small lymphocytes per cubic millimeter; the amount of total protein was 43 mg.; that of sugar 69 mg. and that of sodium chloride 780 mg., per hundred cubic centimeters; the colloidal gold curve was 0022000000, and the Wassermann reaction was negative.

Course.—While in the hospital, the patient continued to have frequent petit mal attacks daily and severe major seizures, which occurred usually in series during a period of several days, with free intervals of several weeks. The series of major seizures were usually preceded by a prodromal period of two or three days, during which emotional instability and neurovegetative disturbances of a "vagotonic" type were prominent. During this period the patient was irritable, uncommunicative, apathetic and somnolent. She complained of being sleepy; the facies was of a pasty gray color; the pupils were small; the pulse was slow, and there were drooling and a great deal of clammy perspiration of the hands and feet.

The major seizures consisted usually of conjugate deviation of the head and eyes to the right, followed by a sustained (tonic) extension spasm of the right arm and leg, while the left arm and leg were usually flexed on the trunk. The spasm was followed by clonic convulsions and resolution of muscular tension. After such severe seizures, weakness of the right arm and leg increased, and for several hours the patient did not use the right hand in holding objects. Speech was inarticulate and thick, and she was not able to comprehend simple questions or to explain her needs.

The petit mal attacks consisted of musclar contractions of the face (grimacing), staring and drooling, followed by sudden collapse, when she dropped to the floor but promptly arose. It was observed that the petit mal attacks and major seizures were particularly likely to occur at the time of, or immediately after, a movement of the bowels.

In August 1934 the patient had a series of seizures, which developed into status epilepticus, and she died of acute edema of the lungs, at the age of 15.

Autopsy.—This was performed eight hours after death. The body was well developed and well proportioned. Except for cyanosis of the face and neck and postmortem discoloration of the dependent surfaces of the body, the integument was clear; the face and sacrolumbar region were free from birthmarks or any visible congenital abnormalities. Examination of the thoracic organs showed severe congestion and edema of both lungs with many hemorrhagic spots and bronchopneumonic foci, especially in the left lung. The thymus gland was in a state of good involution. The mediastinal glands were not pathologic. The heart was normal in size and shape; it weighed 165 Gm. and showed no valvular lesions. The abdominal organs were congested, but otherwise showed no gross pathologic changes. In particular, the kidneys, adrenals and pancreas showed no evidence of tumors or cysts. The liver weighed 965 Gm.

The calvarium was rather thick. The skull cap was adherent to the dura, which was of a normal pearly white color. The pia-arachnoid was distended with clear fluid. A few vascular adhesions were present over the convexity of the hemispheres. The longitudinal sinus was filled with liquid blood. The pia-arachnoid was less transparent than normal; in places it was opaque, and along the longitudinal and sylvian fissures it was milky and adherent to the cortex. The pial blood vessels were congested. The pia over the base of the brain and the basal blood vessels was normal. The brain stem and cerebellum were normal in size and general configuration. The total weight of the brain was 1,245 Gm. The convolutional pattern of the cerebral hemispheres was of a simple type. The gyri of the temporal and frontoparietal lobes bilaterally were somewhat plumper than normal. The sylvian fissure in each hemisphere was deep and long; the gyri of the parietal portion of the operculum were smaller, somewhat firmer than elsewhere and covered with a thickened, opaque, granular pia.

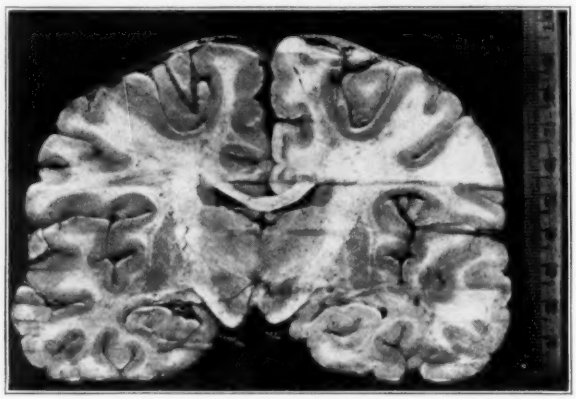


Fig. 2.—Frontal section of the brain, showing lesions characteristic of tuberous sclerosis in the left gyrus cinguli. Note thinning of the cortex and the greater number of dilated blood vessels (dark dots and holes) in the left hemisphere (right in picture).

After fixation in a dilute solution of formaldehyde U. S. P. (1:10), the brain was cut in frontal slabs. The cortex of the left hemisphere was somewhat thinner than that of the right. The centrum ovale, capsula interna and basal ganglia of the left hemisphere were more vascular than the corresponding areas in the right hemisphere. The most striking gross abnormality, however, was in the left gyrus cinguli (fig. 2). The entire middle third of this long gyrus overlying the corpus callosum was unusually large, in places being nearly three times the width of that on the right. The surface of this portion of the left cingulum was irregular, dimpled and covered with transverse striations. Its consistency was firm and leathery. The cortex of the gyrus was white. In the white matter of the cingulum, under the abnormally firm cortex, there was a reddish gray band of softened cerebral tissue. The cerebral ventricles and choroid plexus showed no abnormalities visible to the naked eye; there was no evidence of subependymal tumors; the tuber cinereum appeared thicker and lighter than usual, and the choroid plexus of the left lateral ventricle was thin.

Histologic Examination of the Brain.—A block of the abnormal portion of the left gyrus cinguli was cut in frozen sections and stained by the Cajal silver-pyridine and silver-alcohol-pyridine methods for neurofibrils. A frontal slab of the hemispheres between the anterior and the posterior commissure, including the gyri cinguli, corpus callosum and basal ganglia with the hypothalamus, was embedded in pyroxylin, sectioned and stained by the methods of Loyez and Van Gieson and with hematoxylin and eosin and cresyl violet.

Dilatation of the blood vessels and perivascular spaces was present in all parts of the brain, although somewhat more marked in the left hemisphere. There were many thrombosed veins, with extravasation of blood corpuscles into the dilated perivascular spaces. The thromboses and the congestive phenomena were distinctly more marked in the basal ganglia and thalamus, especially near and about the wall of the third ventricle and in the hypothalamus. In several places over the convexity of the brain small subpial hemorrhages were seen. Nowhere was there observed inflammatory round cell infiltration of the perivascular spaces. Marginal gliosis of the cerebral convolutions was present in many places, and in the cortex of the cornu ammonis on both sides a thick band of glial overgrowth under the pia could be seen with the naked eye. Aside from the acute and chronic degenerative changes, no striking abnormalities were discovered in the cellular and myelin architecture of the cerebral cortex, except in the left gyrus cinguli.

The ependyma of the lateral walls of the third ventricle in a few places showed reduplication and heaping of the lining cells, some of which appeared to migrate from the surface of the ventricle into the underlying cerebral tissue. Abnormality of the histologic structure was particularly conspicuous in the floor of the third ventricle over the infundibulum and tuber cinereum (fig. 3). Here the ependymal cells were proliferated and formed a thick, irregular band of nuclei. Over this band of proliferated ependymal cells was a thick mass of glia nuclei and fibers, among which were many collagen fibers. This spongelike meshwork of fibrous tissue spread over the ependyma on its ventricular side, breaking through the ependymal lining from the lateral walls of the ventricle. Thus, the ependyma appeared to be displaced into the depth of the tuber cinereum. The strands and nests of the proliferated ependymal cells invaded the tuber cinereum. The tuber cinereum in the region of the nucleus ventralis, the wall of the infundibulum and the pituitary stalk were congested and thicker than usual and contained numerous small blood vessels and capillaries which were distended and filled with blood. The nerve parenchyma of this region of the floor of the third ventricle consisted of increased glia fibers and nuclei, but practically no nerve cells were seen. The pia in this region was thickened; in places there was fusion of the pia and the cerebral tissue, which consisted of glial and connective tissue (collagen) fibers. These abnormalities were observed only in the anterior (tuberal) portion of the ventricular floor; posteriorly, in the region of the mamillary nuclei, no striking abnormalities except moderate ependymal proliferation and congestive vascular phenomena were observed.

The abnormality of the left gyrus cinguli, evident in the gross specimen, was conspicuous with Loyez' myelin stain because of the lightness of the cortical and subcortical matter of the gyrus as compared with the neighboring gyri (fig. 4). The tangential fibers and the stripe of Baillarger were not discernible in the cortex. In the subcortical white matter of the gyrus lack of myelin was particularly marked, forming a clear band immediately under the cortex. The abnormality in the vascular supply of the gyrus was striking in that the cortex, usually rich in capillaries and small blood vessels, was here nearly avascular, whereas in the subcortical white matter, especially in the clear demyelinated zone, the capillaries were distinctly in excess of normal.

Fig. 3.—Floor of the third ventricle in the region of the tuber cinereum (nucleus ventralis), showing proliferation and invasion of the tuber by ependymal cells. Note the fibrous overgrowth covering the ependyma, vascular proliferation, congestion and gliosis in the region of the nucleus ventralis tuberi; pial thickening and fusion with the cerebral substance are seen on the right side of the picture.

Left Gyrus Cinguli: The abnormalities in the gyrus may conveniently be described according to their occurrence in three zones. The outer zone of the gyrus, comprising the pia and the molecular layer of the cortex, presented intense marginal gliosis. The pia was thickened. The pial blood vessels, filled with blood, had thick, homogeneous walls, conveying the impression of a certain degree of hyaline change. In many places the proliferated connective tissue and glia fibers formed adhesions between the pia and the marginal glia of the cortex. In some places thick bands of connective tissue and glia fibers penetrated into the cortex from the adhesions (fig. 5). In the molecular layer of the cortex many glia nuclei, but no nerve cells, were present.

The middle zone, comprising the cortex, showed striking abnormalities. The upper part of the gyrus, facing the first frontal convolution above, and the upper half of the medial portion of the gyrus, facing the falx, were entirely devoid of

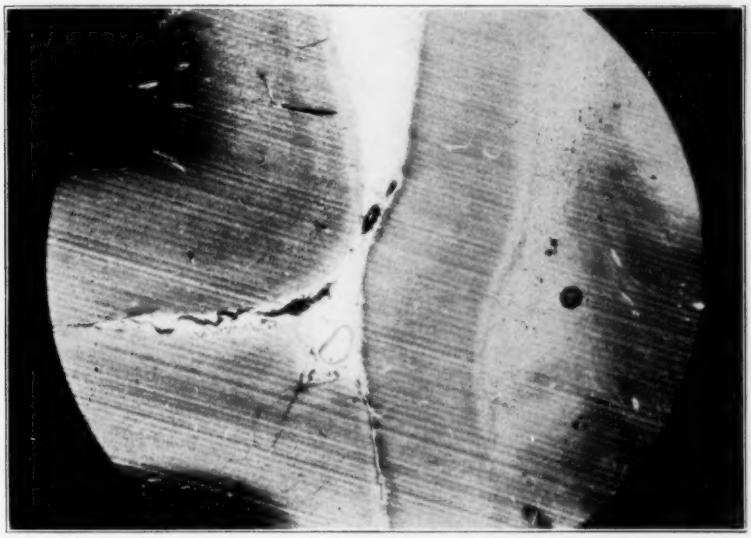


Fig. 4.—Demyelination of the cortical and subcortical matter in the left gyrus cinguli. Note poverty of blood vessels in the cortex and their excess in the subcortical white matter (large blotches are artefacts). Loyez stain.

nerve cells. On the other hand, the lower medial portion and the inferior side of the gyrus, facing the corpus callosum below, contained ganglionic elements, much reduced in number as compared with the symmetric distribution in the cortex of the right (normal) gyrus cinguli but greatly exceeding in size the normal nerve cells (figs. 6 and 7). These cells were most numerous in the deeper parts of the cortical zone; a few were observed in the subcortical white matter. No laminar arrangement of the cells was recognizable; they were strewn about in all directions, in contrast, in this respect, to the orderly polar orientation of the nerve cells in the normal cortex. Examination under a higher power lens revealed that some of these cells showed no distinctive acute or chronic changes except their abnormal size and configuration. They had a clear central nucleus with a dark nucleolus; the cytoplasm was filled with normally distributed tigroid substance However, many of the cells were swollen; the cytoplasm was cloudy or pale;

the nuclei were indistinct and displaced, and a few were distended with large clear vacuoles—probably fat. A great increase in glia nuclei was evident throughout all parts of the cortex. However, nowhere was neuronophagia seen, and, in this connection, it may be stated that the normal satellitic glia nuclei about the giant cells were peculiarly scarce, and often absent. The neurofibrillar methods of Cajal brought the unusual features of the giant nerve cells into full evidence. Examination of the sections at different levels of the gyrus revealed extreme variation in number and irregularity in arrangement of these cells. In some sections they were reduced to a single cell; in others they formed small clusters

Fig. 5.—Marginal gliosis and proliferation of connective tissue and glia with numerous glia nuclei in the molecular layer, but no nerve cells. Van Gieson stain.

of from three to five cells; in others they were strewn in irregular rows. Their processes interlaced, forming a thick meshwork of fibers. They varied greatly in size and configuration; some exceeded by as much as fifteen times the diameter of the normal nerve cells; others were smaller than normal; some were round; others were pear shaped or fusiform; many were curved in the form of a quarter-moon. The axons often divided almost immediately after leaving the cell body into several thin, unusually long secondary branches. The dendrites varied greatly in diameter, some being thick, others thin. Many of the cells had a star-shaped

body, with radial distribution of dendrites, and appeared like large astrocytes; others were spindle shaped, having only one or two processes, and resembled unipolar or bipolar spongioblasts. Many had a round, clear nucleus, poor in chromatin; in others the nucleus had scattered chromatin granules, as in glia nuclei. The intracellular neurofibrils often coalesced and interlaced about the nucleus, forming a

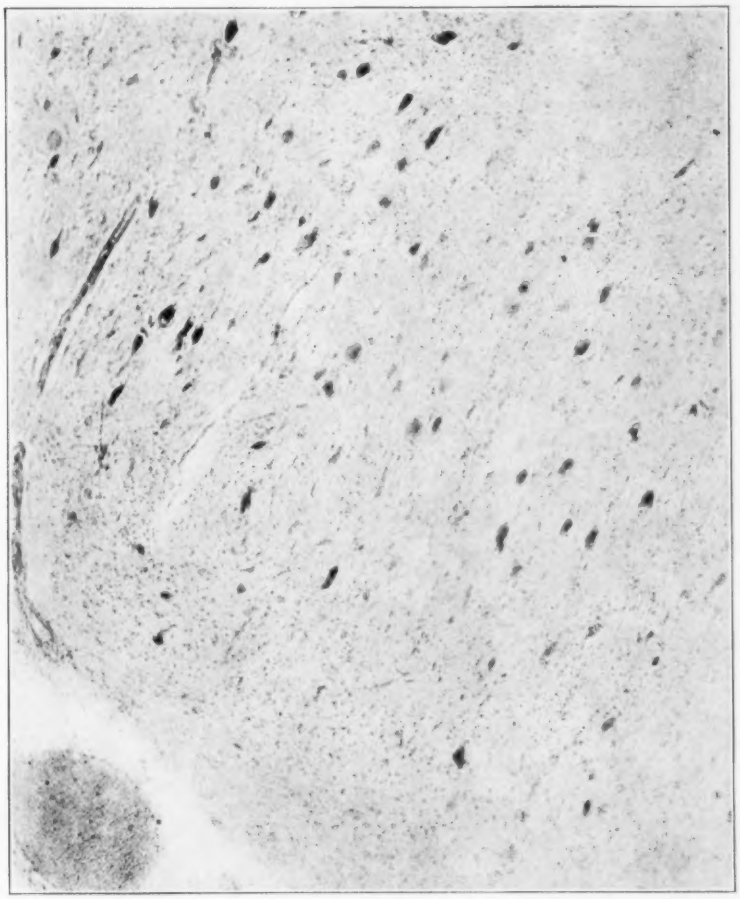


Fig. 6.—Giant nerve cells in the left gyrus cinguli. Cresyl violet stain.

meshwork resembling matted hair. The ground substance of the cortex contained an increased amount of nonmyelinated nerve fibers. The peculiarities in arrangement and configuration of the giant cells are shown in figures 8, 9 and 10.

The subcortical zone of the gyrus, comprising the band of softened cerebral tissue, which in the fresh specimen was observed to be gray and which in sections stained by the Loyez method showed total lack of myelin, appeared in hematoxylin and eosin and Van Gieson preparations to consist of spongy, lightly stained ground

substance with many holes from which blood vessels had fallen out. There were many glia nuclei and dustlike, scattered calcospherites. The latter appeared as granular bodies of concentric structure, with a dark-stained central spherule. Among the glia nuclei, on the cortical side of the band of softening, were many unusually large, round or oval cells with homogeneous protoplasm and an eccentric nucleus

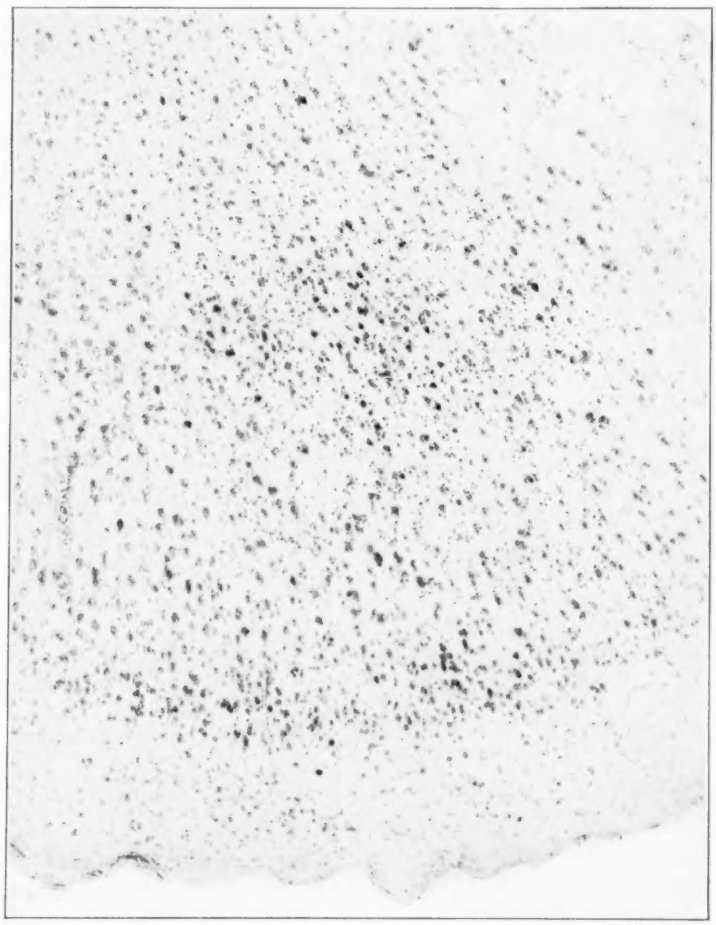


Fig. 7.—Symmetric area in the right gyrus cinguli (same magnification as that in fig. 6), showing contrast in the cytoarchitecture to that of the left gyrus. Compare the orderly arrangement of cell layers and cell orientation with the pattern in figure 6.

rich in chromatin pressed to one side of the cell (fig. 11). In silver preparations it was seen that these cells had one or two polar prolongations and, save for lack of neurofibrils, resembled in size and shape the large nerve cells in the cortex. In the zone of transition between the cortex and the subcortical band of softening these large cells intermingled with giant nerve cells, and in some instances it was

difficult to distinguish between the two types. However, the size, position and appearance of the nuclei in the Van Gieson and hematoxylin and eosin preparations conveyed the impression that they were cells of glial stock rather than nerve cells.

It was a characteristic feature of the lesion that in many places, especially in the marginal zone and in the cortex, the silver impregnations for neurofibrils

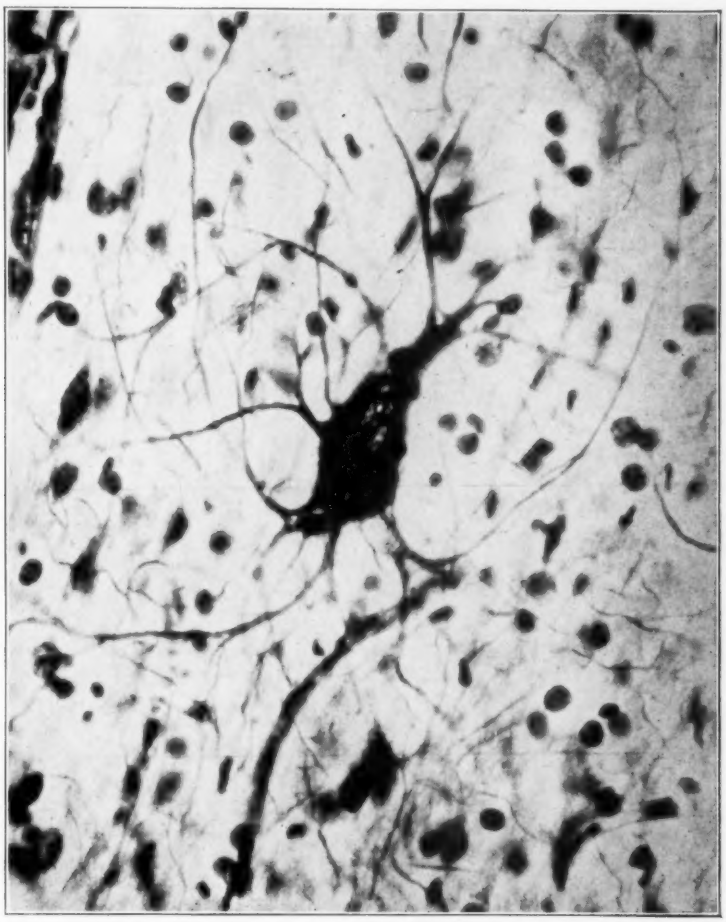


Fig. 8.—A single giant nerve cell, showing unusual number and length of processes.

brought into evidence the astrocytic glia. In the subcortical softening the axis-cylinders were rarefied, but not destroyed.

Comment on Pathologic Changes in the Brain.—The gross appearance of the abnormal portion of the gyrus cinguli was characteristic of tuberous sclerosis. Histologic examination of the sections showed also

that all the essential features of this lesion were present, namely: profound confusion of the cortical cytoarchitecture confined to a portion of the gyrus; the presence of malformed nerve cells, so unique in gigantic size and unusual configuration that they alone established the diagnosis; excess of nonmyelinated nerve fibers and fibrous glia in the

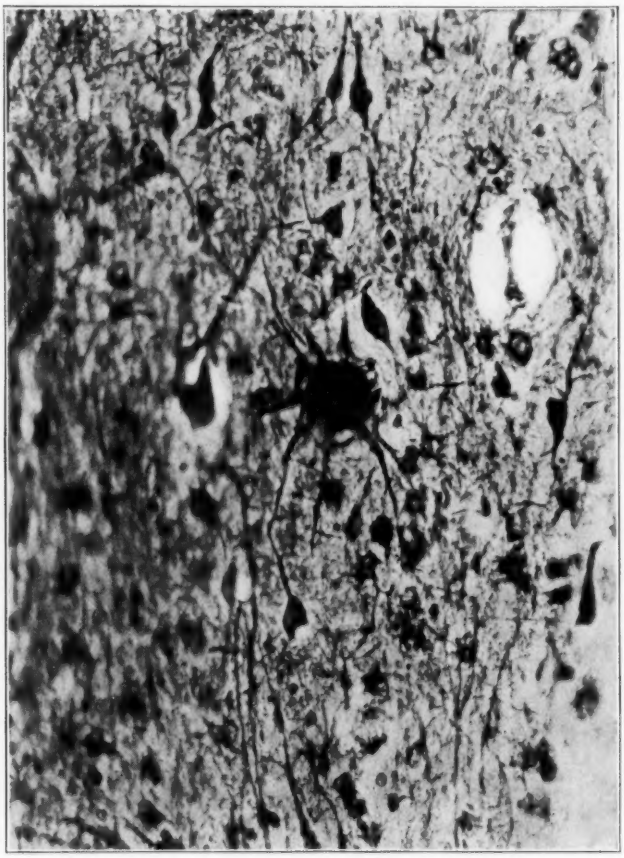


Fig. 9.—A giant nerve cell resembling a large astrocyte.

ground substance of the marginal zone of the cortex and in the white matter of the gyrus; the presence of unusual "large" cells in the cortex and in the periphery of the rarefied subcortical zone of the white matter, and reversal of the normal angioarchitecture of the affected gyrus, viz., poverty of vascular supply in the cortical zone and excess of blood vessels in the subcortical white matter of the gyrus.

The work of Hartdegen,[4] Pelizzi, Vogt,[5] Orzechowski and Nowicki,[6] Bielschowsky and Gallus [7] and many other neuropathologists has provided a rich stock of information on the histopathologic features and pathogenesis of tuberous sclerosis. It is now generally admitted that the condition is a congenital malformation originating in early fetal life—possibly a defect in the germ plasm—and leading to blastomatous transformation of certain elements of the ectodermal layer of the embryo. This congenital ectodermal defect may manifest itself in developmental abnormalities of all or several derivatives of this layer: the skin, the retina, certain endocrine glands and especially the central nervous system. The condition may be considered as a malformation of neoplastic type. The potentiality of true tumor formation is, indeed, a prominent feature of tuberous sclerosis, which it shares with Recklinghausen's disease and certain forms of angiomatosis, e. g., Lindau's disease.[8] Many patients die with signs of intracranial tumor,[9] of which tumors of the ventricle are most frequent. The congenital neoplastic malformations in the nervous system, as elsewhere in the body, are usually multiple. Bielschowsky spoke of the condition as "blastomatosis disseminata." [7a] However, the abnormality may be discrete and confined to one convolution, as in the present case.

The observation of neoplastic proliferation of the ependymal cells, with gliosis in the floor of the third ventricle, confined to the region of the infundibulum and tuber cinereum, i. e., to the rostral part of the hypothalamus, is of interest. These histologic abnormalities suggest an early stage of tumor of the ventricule. In this connection, it may be pointed out that in cases of typical ventricular tumor associated with tuberous sclerosis, the proliferative ependymal reaction is usually most marked when the neoplastic activity is particularly energetic. In figure

4. Hartdegen, A.: Ein Fall von multipler Verhärtung des Grosshirns nebst histologisch eigenartigen harten Geschwülsten der Seitenventrikel ("Glioma gangliocellulare") bei einem Neugeborenen, Arch. f. Psychiat. **11**:117, 1881.

5. Vogt, H.: Zur Pathologie und pathologischen Anatomie der verschiedenen Idiotieformen: II. Tuberöse Sklerose, Monatschr. f. Psychiat. u. Neurol. **24**:106, 1908.

6. Orzechowski, K., and Nowicki, W.: Zur Pathogenese und pathologischen Anatomie der multiplen Neurofibromatose und der Sclerosis tuberosa (Neurofibromatosis universalis), Ztschr. f. d. ges. Neurol. u. Psychiat. **11**:237, 1912.

7. (*a*) Bielschowsky, M., and Gallus: Ueber tuberöse Sclerose, J. f. Psychol. u. Neurol. (supp. 1) **20**:1, 1913. (*b*) Bielschowsky, M.: Zur Histopathologie und Pathogenese der tuberösen Sklerose, ibid. **30**:167 1923-1924.

8. Lindau, A.: Studien über Kleinhirncysten: Bau, Pathogenese und Beziehungen zur Angiomatosis retinae, Acta path. et microbiol. Scandinav., 1926, supp. 1, p. 1. Footnote 1.

9. Globus, J. H.: Neurinome centrale associé à une sclérose tubéreuse (neurospongioblastose disseminée), Rev. neurol. **59**:1, 1933.

12, a section from a tumor of this kind occurring in another case shows the extreme proliferation of ependymal calls which invade the underlying cerebral tissue. The analogy with the histologic picture in the wall and floor of the third ventricle in the present case (fig. 3) suggests that a tumor would have developed in this location if the patient had lived longer.

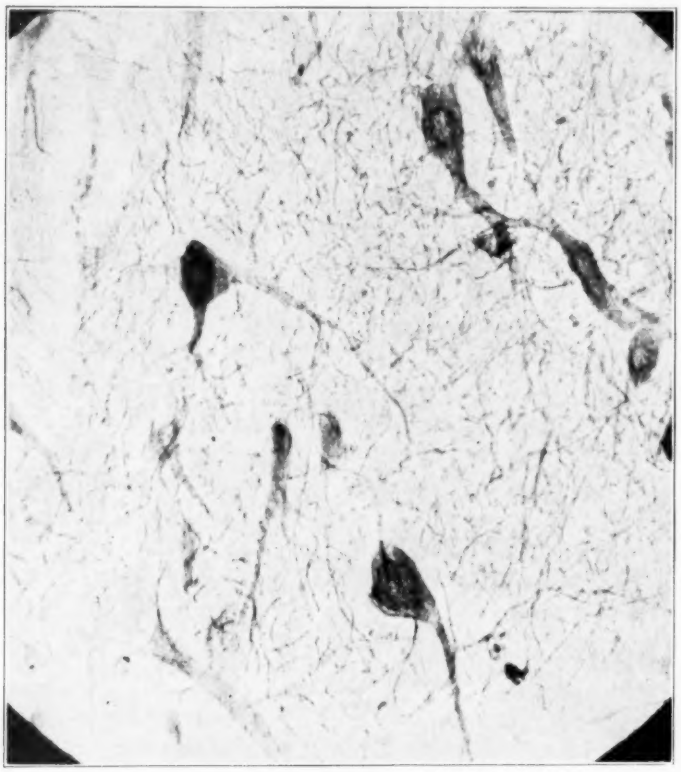


Fig. 10.—Cluster of giant nerve cells showing matted neurofibrils about the nucleus. Note the peculiar configuration of the cell bodies and processes.

The other abnormalities in the brain in this case—namely, the marginal gliosis, chronic and acute degenerative changes in the nerve cells of the cortex and congestive vascular phenomena—are secondary lesions common in cases of chronic epilepsy and must be attributed to the circulatory disturbances associated with seizures.[10] Dilatation of

10. Tramer, M.: Untersuchungen zur pathologischen Anatomie des Zentralnervensystems bei der Epilepsie, Schweiz. Arch. f. Neurol. u. Psychiat. **2**:202, 1918. Spielmeyer, W.: Die Pathogenese des epileptischen Krampfes, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:501, 1927. Minkowski, M.: Zur pathologischen Anatomie und Pathogenese der Epilepsie, Jahrb. f. Psychiat. u. Neurol. **51**:134, 1933.

the blood vessels and capillaries and venous thrombosis with extravasation of blood into distended perivascular spaces were especially prominent in the basal ganglia, near and about the third ventricle and in the hypothalamus. They are to be explained as a result of acute venous stasis during the agonal period in a patient who died in status epilepticus.

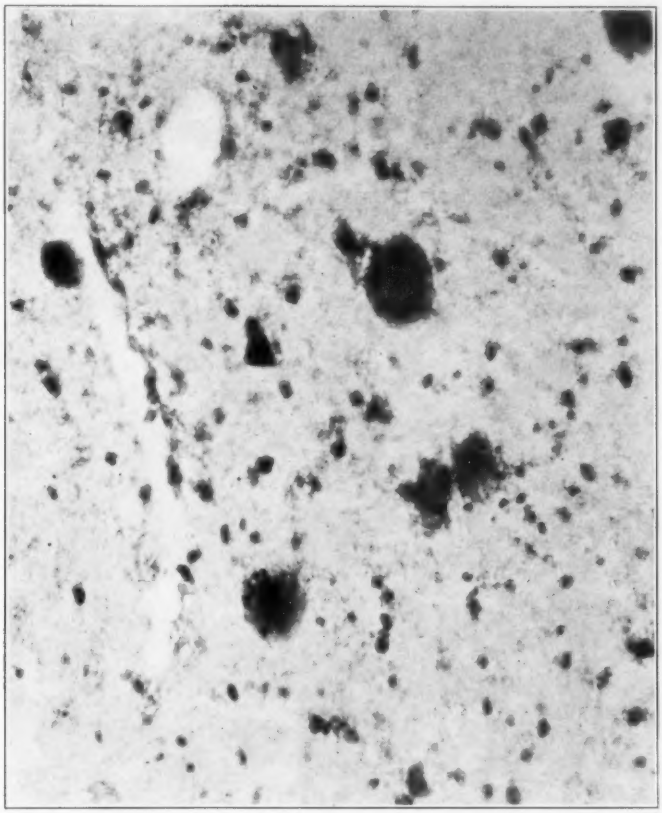


Fig. 11.—Large glia-like cells in the subcortical zone of softening.

CORRELATION BETWEEN CLINICAL SYMPTOMS AND PATHOLOGIC CHANGES

It was a significant fact in the family history of the patient that of the mother's six pregnancies one was ectopic and three ended in early miscarriage. It is probable that between the disturbance of the gestative function in the mother and the congenital defect in the patient there existed a pathogenetic relationship. Whatever may be the cause of cerebral maldevelopment, it must have occurred during early embryonic life. However, it did not manifest itself until later childhood,

when epilepsy and associated mental disturbances appeared. Delayed manifestation of congenital abnormalities is frequent in cases of tuberous sclerosis. This clinical feature stands in definite relation to the blastomatous character of the congenital malformation, which may remain latent for years and may never manifest itself, but which may

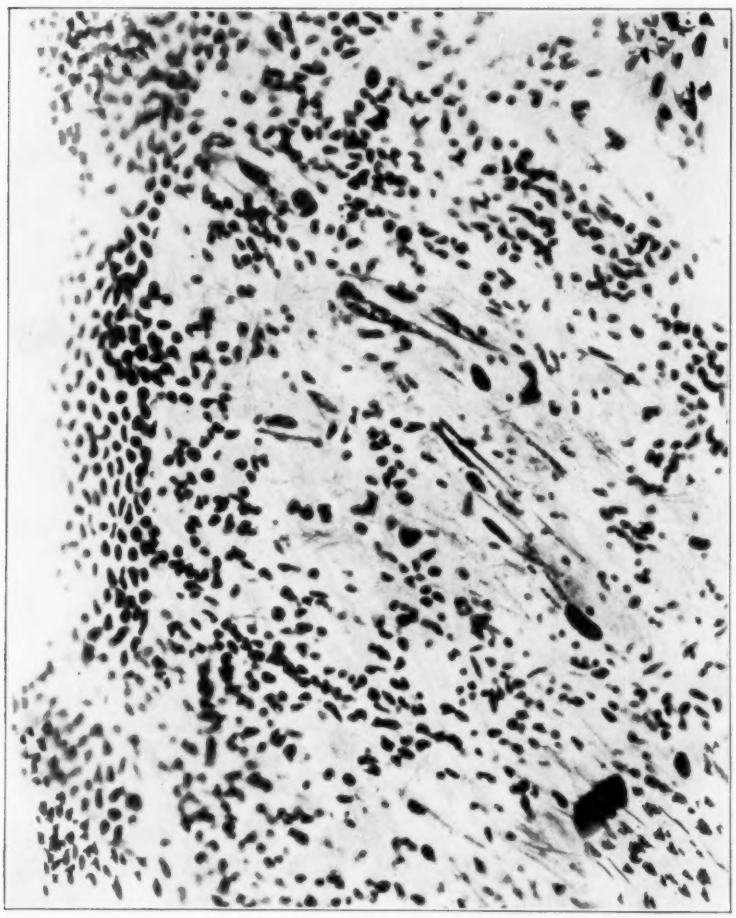


Fig. 12.—Proliferation and migration of ependymal cells in a tumor of the ventricle in a case of tuberous sclerosis (compare with fig. 3).

reveal its evolutive tendency at any time, as is characteristic of blastomatous (neoplastic) processes in general.[7] If clinical symptoms do not reveal the condition at birth, the critical period appears to be later childhood and puberty. This holds true also for the cutaneous congenital anomalies—the multiple sebaceous adenomas of the face—which may appear suddenly at the age of 12 or later and reveal the

symptomatic significance of the coincident epilepsy and mental deficiency, which otherwise would be called "idiopathic" or be attributed to an altogether unrelated factor, such as "psychic trauma."

The following points were outstanding in the clinical condition of this patient: (1) the neurovegetative disturbances of "vagotonic" type which appeared during the prodromal period preceding the series of major seizures and were characterized by increased somnolence, vasomotor disturbances, sweating of the hands and feet, drooling, bradycardia and increased peristalsis, with call to defecation at or about the time of occurrence of the seizures; (2) the changes in personality characterized by extreme instability of mood with periodic abnormal irritability, apathy, sleepiness and dulling of mental faculties, all of which progressed rapidly and eventually led to a characteristic picture of epileptic deterioration, and (3) the epileptic seizures characterized by the tendency of the convulsive phenomena to lateralize toward the right side of the body (conjugate deviation to the right, tonic spasm of the right arm and leg) and followed by transitory hemiparesis of the right arm and leg with dysarthria and signs of aphasia. There was an interrelationship of these three categories of symptoms suggesting disturbance of one and the same mechanism. The disturbances in the sphere of vegetative (interofective) innervation were in the foreground. They dominated the clinical picture during the prodromal period preceding the seizures. These disturbances point to an abnormality in the autonomic regulation of the steady state of the internal medium and of the reflex activity of the cerebrum, as shown by the emotional instability of the patient, the progressive intellectual deterioration and the tendency to paroxysmal dissolution of cerebrospinal (exterofective) functions, with loss of consciousness, convulsions and postparoxysmal paralysis and aphasia.[11]

It is noteworthy that the developmental abnormalities in this case, as in many other cases of tuberous sclerosis, occurred in the gyrus cinguli and in the rostral part of the third ventricle; i. e., in the parts of the brain to which higher autonomic functions are usually assigned. One may assume that the disturbances in the sphere of neurovegetative innervation in this case were related to these congenital developmental abnormalities of the brain. It was the left hemisphere which showed evidence of a discrete malformation, and it was in this hemisphere that the cumulative effects of chronic circulatory disturbances were most evident, clinically and histologically.

---

11. Yakovlev, P. I.: Neurologic Mechanism Concerned in Epileptic Seizures, Arch. Neurol. & Psychiat. **37**:523 (March) 1937.

FUNCTIONAL IMPLICATIONS OF CONGENITAL MORPHOLOGIC ABNORMALITIES IN THE NERVOUS SYSTEM AND THEIR BEARINGS ON PATHOGENESIS OF EPILEPSY

The general functional implications of developmental defects, bearing especially on the neuroectoderm, should be obvious. In this connection, the work of Minkowski and of von Monakow's school [12] is of particular interest. Minkowski demonstrated in the living human fetus at various ages of gestation the intimate interdependence in time relationship of the successive phases of structural evolution of the nervous system and the successive phases of development of reflex action. Before the third month of gestation—aneural phase—reflex action, in the proper sense of the word, does not exist. From the third month on the reflex arcs become established. However, the reflex patterns are simple and are elicited as independent units, without integration with each other. Gradually, with the myelination of the fasciculi proprii of the spinal cord and of longer tegmental tracts, they become integrated into increasingly complex compounds, revealing thus the reflex patterns of higher order. The outstanding feature of reflex integration in the fetal nervous system is its extreme instability. The reflex patterns break down into the simpler, more elementary components whenever there occurs the least disturbance in the steady state of the internal medium (lack of oxygen supply, chilling of the fetus). The instability of the state of the internal medium is a well known trait of the fetus and of the newborn infant. Reflex regulation of the steady state of the internal medium (homeostasis) by the autonomic nervous system is a later, in many respects a postnatal, acquisition. In connection with these data concerning the embryogenesis of the integrative functions of the nervous system, it is easy to conceive that an impediment in the process of morphologic differentiation of the nervous system must disturb the time relation between the successive phases of the development of nervous integration from the loosely connected elementary reflex patterns of the fetus to the intimately coalescent, simultaneous and successive combinations of the complex reflex patterns of the mature organism. There is, as a result, a congenital fragility, i. e., a lack of coalescence in time, of reflex action, persisting into postnatal life. The epileptic seizure may be regarded as a pertinent example of such congenital fragility of nervous integration in certain persons. Indeed, the epileptic seizure reveals two fundamental traits of the nervous system reminiscent of the fetal state: first, the deficiency of neurovegetative regulation of the steady state of the internal medium, with a

12. (*a*) Minkowski, M.: L'état actuel de l'étude des reflexes, Paris, Masson & Cie, 1927. (*b*) von Monakow, C., and Mourgue, R.: Introduction biologique à l'étude de la neurologie et de la psychopathologie, Paris, Félix Alcan, 1928.

readily resulting state of vegetative "diaspasis" (vasomotor instability, prodromes, aura), and, second, the paroxysmal dissolution of the cerebrospinal functions into lower, more elementary, reflex patterns, i. e., an abnormal tendency to paroxysmal "diaschisis" (loss of consciousness, convulsions, coma and postparoxysmal paralysis).[11] As the persistent embryonal traits in the structure of the maldeveloped nervous system represent morphologic "anachronisms," so the embryonal traits in the function of such a nervous system may be considered as the manifestations of functional "anachronisms."[12b]

From the standpoint of the pathogenesis of epilepsy, the study of tuberous sclerosis is of interest, for this congenital condition is a striking example not only of a defective structural formation but of defective functional integration of the nervous system, predisposing to epilepsy. Indeed, while in most other conditions epilepsy is a facultative symptom, in tuberous sclerosis it is nearly obligatory, at least during some time in the life of the patient. There must, therefore, be something specific in the nature of this condition to make it so eminently epileptogenic. In this respect, the blastomatous character of the malformation, endowed with evolutive potentialities of a new growth, must play a role. It is the preferential localization of the blastomatous nests along the zone of cleavage between the telencephalon and the diencephalon that appears to be especially significant. If one considers from the developmental point of view the medial wall of the cerebral hemispheres, with the gyrus cinguli, hippocampal gyrus, striothalamic sulcus and rostral portion of the third ventricle, it becomes apparent that these areas on the outer and the ventricular surface of the brain correspond in the prosencephalic vesicle to the zone along which the cleavage between the telencephalon and the diencephalon takes place, namely, to the sulcus hemisphericus and the sulcus terminalis. The gyrus cinguli and hippocampus with the rhinencephalon develop along the telencephalic lip of the sulcus hemisphericus, which already in the embryo of 6 mm. clearly marks off the future hemispheres, rostrally and laterally, from the diencephalon, caudally and medially.[13] On the inner surface of the wall of the prosencephalic vesicle the zone of cleavage corresponds to the sulcus terminalis. In embryos from 10 to 20 mm. this sulcus is nearly perpendicular to the sulcus limitans (of Monro) and separates the striatum, the rostral part of the hypothalamus and the lamina terminalis, with the commissural plate, all of which belong to the telencephalon and are rostral to the sulcus terminalis, from the thalamus and pars mamillaris hypothalami, which are caudal to the sulcus and belong to the diencephalon. As a result of rapid growth of the hemi-

13. Hochstetter, F.: Beiträge zur Entwicklungsgeschichte des menschlichen Gehirns, Vienna, Franz Deuticke, 1929.

spheres, the striatum shifts its position and, instead of being rostral, becomes rostrolateral to the thalamus, and the sulcus terminalis, instead of being nearly perpendicular to the sulcus limitans, becomes nearly parallel.[13] In the adult brain the sulcus is clearly shown as a deep groove separating the caudate nucleus from the thalamus and is known as the sulcus striothalamicus. It is shown in figure 1 to be studded with spongioblastic tumors, which project into the lateral ventricle. It is generally recognized that in the nervous system, as elsewhere in the body, malformations are especially likely to occur in the parts in which the processes of differentiation and spatial orientation of tissues are particularly active, i. e., along the zones of cleavage and of fusion of ontogenetically different parts of the organs.[1b] The preferential localization of the tuberosclerotic nests on the medial wall and base of the hemisphere near the midline and along the sulcus terminalis and rostral part of the hypothalamus is a typical example of this teratologic principle. Applying the general functional implications of developmental defects of the nervous system, presented at the beginning of this paragraph, specifically to the neoplastic malformation of the brain in tuberous sclerosis, one is led to assume that the malformation along the zone of cleavage and differentiation of the telencephalic and the diencephalic reflex mechanism is responsible for the dissociation in time of development of reflex patterns at these two levels (functional anachronisms). Hence, there results dissociation in the rhythm and rate, i. e., lack of coalescence in time (functional dyschronisms) of the respective reflex activities of these two levels. The psychic abnormalities; the emotional instability; the peculiar "epileptoid" personality traits;[14] the diffuse and varied neurovegetative disturbances of the prodromal period, and, now and then, the paroxysmal cerebral "dysrhythmia" [15] in the form of a petit mal attack, a fit of psychomotor automatism or a major epileptic seizure, with profound dissolution of cerebrospinal functions,[11] may all be explained on the basis of congenital malformation in the critical zone of differentiation of the reflex mechanisms at the highest levels of nervous integration. In the case of tuberous sclerosis, such an interpretation of the relation between the nature and localization of the cerebral malformation and the epilepsy, as the foremost clinical symptom of the condition, is supported by morphologic evidence. How much of such evidence could be disclosed in cases of so-called genuine epilepsy

14. Minkowska, F.: Charakterologische Probleme im Lichte psychiatrischer und geneologischer Hereditätsforschung (mit besonderer Berücksichtigung der Epileptoidie), Ztschr. f. d. ges. Neurol. u. Psychiat. **82**:199, 1923; La constitution épileptoide et le trouble générateur de l'épilepsie essentielle, Evolut. psychiat. **1**:69, 1932.

15. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Epilepsy: Paroxysmal Cerebral Dysrhythmia, Brain **60**:377 (Dec.) 1937.

is an open question. Nevertheless, the possibility that the basis of idiopathic epilepsy is a congenital functional, and therefore structural, malformation of a specific reflex mechanism in the brain has occurred to many who have had occasion to study a large number of epileptic persons clinically and at autopsy.[16]

16. Wohlwill, F.: Entwicklungsstörungen des Gehirns und Epilepsie, zugleich ein Beitrag zur pathologischen Anatomie und Genese der Heterotopien grauer Substanz, Ztschr. f. d. ges. Neurol. u. Psychiat. **33**:260, 1916. Pollak, E.: Anlage und Epilepsie, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **23**:119, 1922.

SPECIAL ARTICLES

MENINGIOMAS OF THE BRAIN

GILBERT HORRAX, M.D.
BOSTON

The meningiomas, or dural endotheliomas, as they used to be called, represent one of the benign, and therefore hopeful, types of tumor of the brain. They are encapsulated growths, attached to some portion of the dura, falx or tentorium, and assume shapes varying from a smoothly elliptic to a highly irregular and nodular form, or even a flat plaque of tissue which is only a few millimeters in thickness. The term "meningioma" was introduced by Cushing [1] in 1922, and no better description of the type of growth indicated can be given than that used by him at the time.

> This word [meningioma], consequently, will be used to indicate the entire group of tumors which appear to arise from the pachymeninx; whether the overlying bone shows hyperostosis or is unchanged; whether the growth is pedunculated or flat and widespread, and regardless of the degenerative changes and the presence or otherwise of psammoma granules.
>
> These tumors, the meningiomas, have, as we shall see, favorite seats of origin, and though they may differ considerably in their histological picture (fig. 1), they are, as a rule, easily recognizable not only by their gross appearance, but because of the fact that the stalk from which in their simpler form they seem to arise is so intimately incorporated with the dura that they appear to originate from it.

In various series of verified tumors of the brain, the meningiomas represent approximately from 12 to 20 per cent of intracranial growths. Ordinarily, they can be wholly removed and do not recur if removal has been complete. Their extirpation, however, is fraught with many difficulties, due particularly to the excessive vascularity of all the tissues surrounding them, their frequent attachment to the large venous sinuses and the relative inaccessibility of growths in certain situations. Much has been written about the meningiomas, since they were the first tumors of the brain to be attacked successfully by surgical measures. Even with all modern aids for operation on the brain, removal of some meningiomas is today a formidable task, as emphasized by Cushing [2] as late as 1932.

Clinical Lecture at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 14, 1938.

From the Department of Neurosurgery, the Lahey Clinic, and the New England Deaconess and New England Baptist Hospitals.

1. Cushing, H.: The Meningiomas (Dural Endotheliomas): Their Source and Favored Seats of Origin, Brain **45**:282, 1922.

2. Cushing, H.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

Two stage operations are necessary in certain instances; a donor for blood transfusion should always be at hand, and it is well, if possible, to have fresh muscle in readiness, taken either from the patient or from another patient who is being operated on in an adjoining room. It is not within the scope of this paper to go into elaborate detail concerning the operations. Some hint has just been made with respect to the preoperative preparations. The operation itself at times may be relatively simple, or it may tax all the resources of the neurosurgeon and his organized team. The length of an operation may vary from an hour or two, in the case of the simplest forms, to as much as six or seven hours, as has occurred in my clinic, in the case of large growths which arise from the olfactory groove and extend under both frontal lobes.

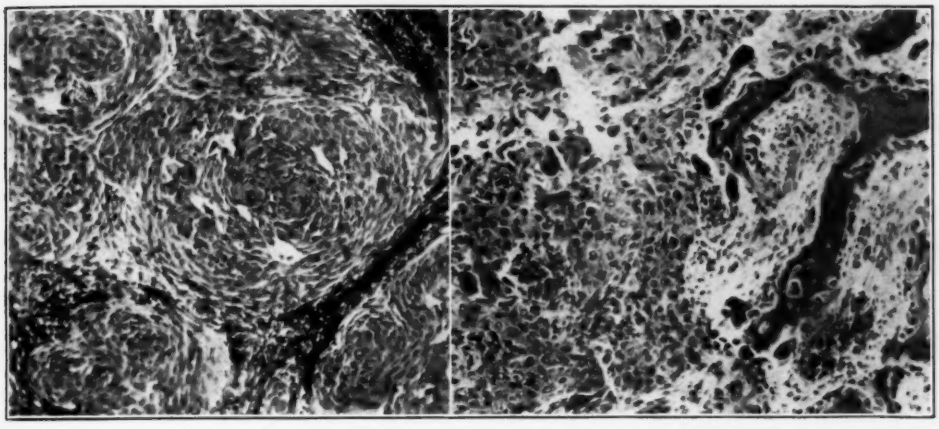


Fig. 1.—At the left, the typical histologic picture of a meningioma, showing characteristic whorl formation. At the right, invasion of bone by cells of the meningioma, a frequent occurrence in certain situations.

DIAGNOSIS

A meningioma may be suspected if a patient with a presumed tumor of the brain gives a history extending over a considerable period, perhaps a year or more. On the other hand, the only apparent evidences of trouble in some instances may go back but a few months. Roentgenograms in cases of these growths are important and valuable because, more than any other intracranial tumors, meningiomas cause definite and recognizable changes in the bone. This feature will be considered in more detail when the various groups of meningiomas are discussed. It may be said, however, that Sosman and Putnam,[3] from a review of Cushing's

3. Sosman, M. C., and Putnam, T. J.: Roentgenological Aspects of Brain Tumors: Meningiomas, Am. J. Roentgenol. **13**:1, 1925.

material, pointed out that the local changes around meningiomas in the order of their importance are: "(1) erosion and vascularity; (2) osteomatous changes; (3) spicule formation; (4) diffuse thickening; (5) enlargement of the meningeal channel, and (6) calcification." Recently, Schwartz [4] has also given an excellent résumé of the roentgenologic findings characteristic of the meningiomas.

Some of the tumors require ventriculographic examination for their localization; others have such a well defined clinical syndrome that their site and pathologic nature may be predicted almost certainly. Cushing segregated various groups of this kind, and Foster Kennedy described the symptom complex in cases of meningiomas arising from the olfactory groove. It is well known that any tumor of the brain adjacent to the rolandic area may cause jacksonian seizures on the opposite side, either with or without symptoms of increased intracranial pressure. Meningiomas are particularly likely to cause such attacks if they occur in this situation.

In a review of the clinical and pathologic aspects of these growths in a series of 75 cases, Frazier and Alpers [5] stressed the fact that most of the tumors were located over the anterior half of the brain, over one half being either frontal or precentral. It is interesting, however, that mental symptoms were lacking in three fifths of their cases. The anterior situation of meningiomas as given by these authors agrees entirely with the observations in my series.

GROUPS BASED ON LOCATION

As there are favorite sites at which meningiomas tend to grow, these tumors may perhaps be discussed most profitably in groups according to their occurrence in these situations (table). The present series

Distribution of 60 Meningiomas According to Location

Situation of Tumor	Number of Cases
1. Over cerebral convexities	24
2. Suprasellar	2
3. Olfactory groove	5
4. Orbitotemporal	9
5. Bilateral, extending across sagittal sinus	4
6. Arising from falx	5
7. Replacing pineal body	1
8. Intraventricular	1
9. From sheath of gasserian ganglion	1
10. Cerebellar	4
11. Multiple	4
Total no.	60

4. Schwartz, C. W.: The Meningiomas from a Roentgenological Standpoint, Am. J. Roentgenol. **39**:698, 1938.

5. Frazier, C. H., and Alpers, B. J.: Meningeal Fibroblastomas of the Cerebrum: Clinicopathologic Analysis of Seventy-Five Cases, Arch. Neurol. & Psychiat. **29**:935 (May) 1933.

of 60 cases, although not large, includes, nevertheless, instances of almost all types of meningiomas in their various intracranial localities.

GROUP 1.—*Tumors Occurring over the Cerebral Convexities, with Their Dural Attachment Often at or Near the Sagittal Sinus.*—As may be expected, by far the largest number in the series (24 tumors) occurred in this group (fig. 2). On the whole, they tended to be in the anterior or central, rather than the posterior, area. A considerable number caused either focal or generalized convulsions, many without the slightest evidence of increased intracranial pressure. Certainly, in three fifths of the cases the diagnosis of a meningioma should have been made from the bony and vascular changes in the skull as shown in the roentgenograms. Typically, such a lesion consists of a circular area of thickened bone projecting inward, with spicule-like radiations from its

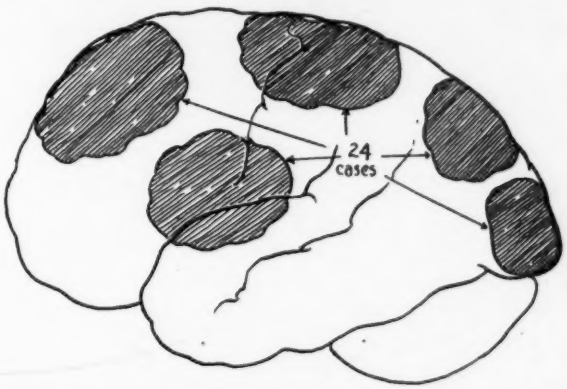


Fig. 2.—Schematic representation of the common sites over the cerebral convexities of tumors in group 1.

periphery. The vascular channels in the bone lead to this area and include an enlarged channel of the meningeal artery, as well as channels of other blood vessels that are not normally present (fig. 3). When roentgenographic evidence is lacking and there are no localizing features, ventriculograms must be made. These show the displacement of ventricles characteristic of tumors in various areas along the parasagittal region. Meningiomas in this region are especially likely to flatten the body of one ventricle from above downward (fig. 4). In 2 of my cases the tumors showed considerable calcification, and in 1 of these, the growth, although large, caused no ventricular distortion (fig. 5).

Meningiomas in this group, as a rule, are the easiest to remove because they are the most accessible (figs. 6 and 7). Even so, some of the smallest and simplest tumors may be surrounded by such vascular tissues, particularly the bone and dura, that it is only after reaching the growth itself that enucleation is simple. There has been only 1 death

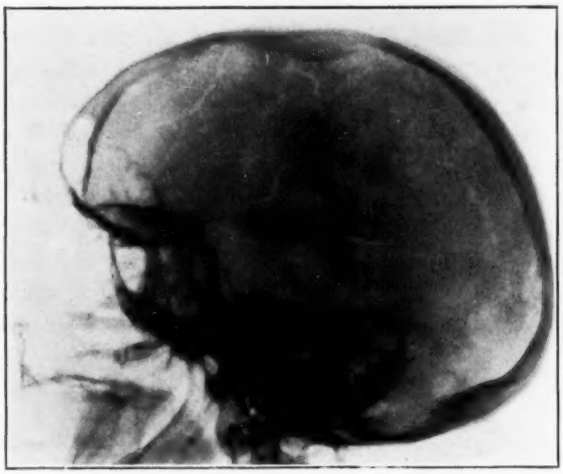


Fig. 3.—Roentgenogram showing a parasagittal meningioma with enostosis at the vertex, to which leads increased vascularity.

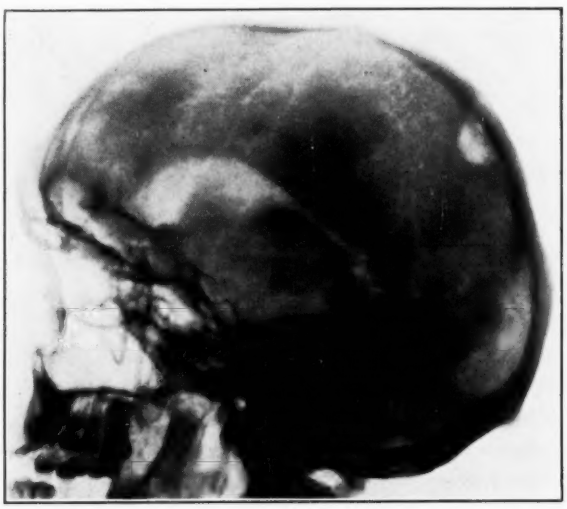


Fig. 4.—Typical flattening and downward displacement of the lateral ventricle caused by a parasagittal meningioma of the parietal region.

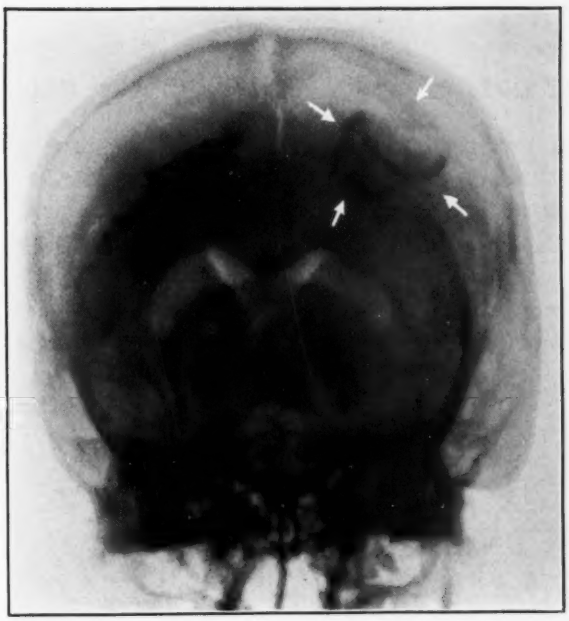


Fig. 5.—Calcified occipital meningioma, which has produced only slight flattening of the posterior horn of the ventricle.

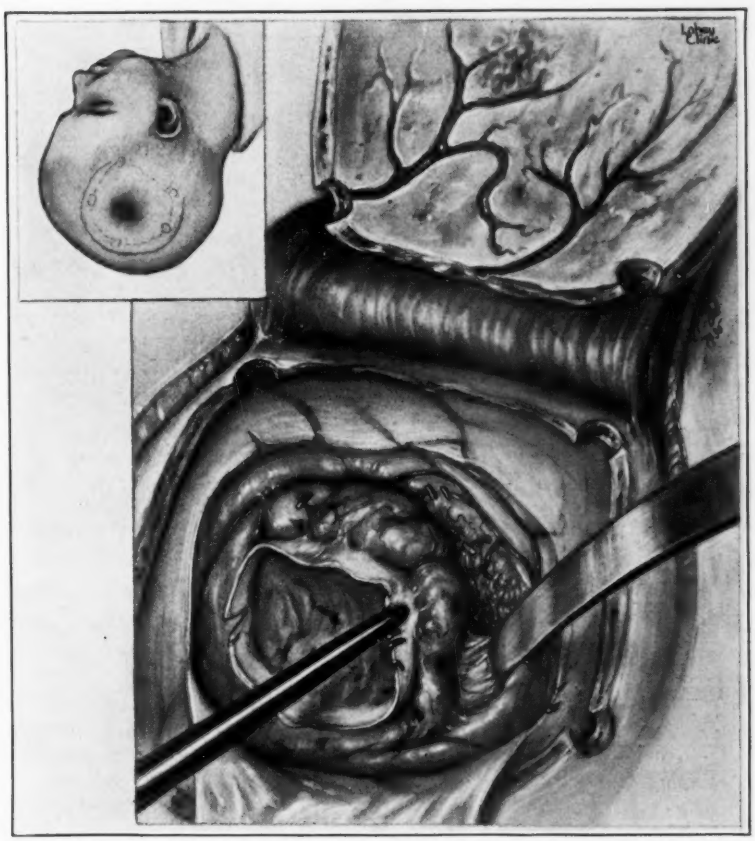


Fig. 6.—Early stage in the removal of a surface meningioma. The dura surrounding the growth has been incised and is used to lift the tumor gently outward as it is freed from the surrounding cortex. Silver clips are placed on entering vessels. Large vascular channels are shown in the bone flap.

among patients with tumors belonging to this group, thus substantiating the well known observation that tumors situated over the convexities are the most favorable from the standpoint of operation.

GROUP 2.—*Suprasellar Meningiomas.*—These are relatively small, often nodular, tumors, which are rounded and arise from the tuberculum sellae between anterior clinoid processes (fig. 8). In this series there were 2 cases of tumor in this situation. Since suprasellar meningiomas

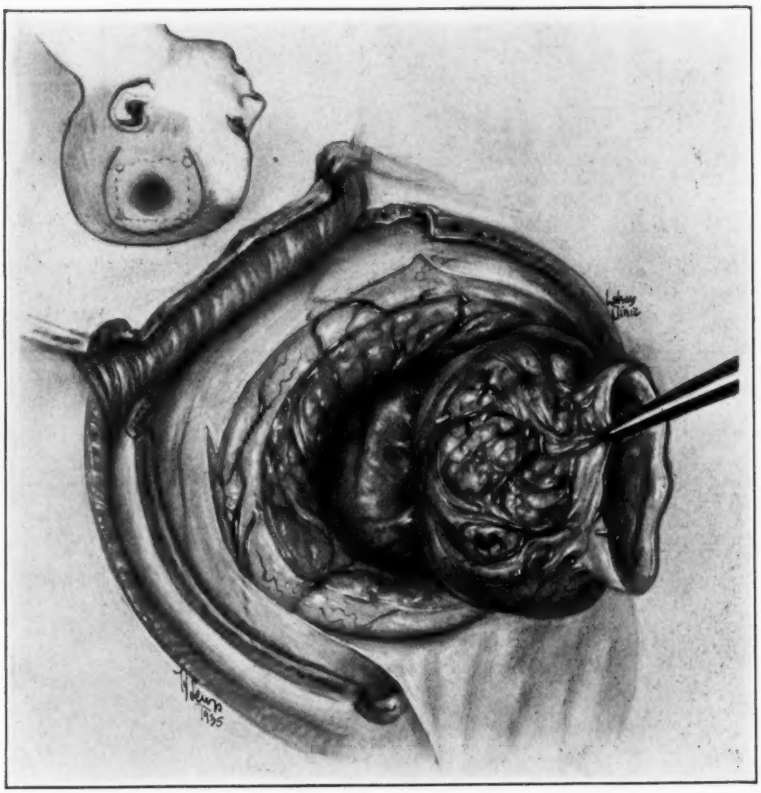


Fig. 7.—Final stage in removal of a meningioma on the cerebral convexity. The growth is being tilted out of its bed by lifting on its dural attachment. Silver clips are placed on entering vessels.

occur in much the same area as do pituitary adenomas and compress the medial surfaces of the optic nerves, the field changes are similar to those associated with lesions of the pituitary. Cushing [6] has called

6. Cushing, H., and Eisenhardt, L.: Meningiomas Arising from the Tuberculum Sellae, with the Syndrome of Primary Optic Atrophy and Bitemporal Field Defects Combined with a Normal Sella Turcica in a Middle-Aged Person, Arch. Ophth. **1**:1 (Jan.) 1929.

attention to the typical syndrome of a suprasellar meningioma. Given a patient in middle adult life showing primary atrophy of the optic nerves and changes in the visual fields suggesting bitemporal hemianopia, but without marked pituitary disturbances or enlargement of the sella, the chance is great that the patient has a meningioma above the sella turcica. In addition, the roentgenogram of the skull almost always shows thickening or heaping up of bone at the tuberculum sellae. One of my patients with a tumor of this type is back at her normal activities with definite improvement in vision, but the other, while able to do much at home, came to the clinic after so much vision had been lost that none was regained.

GROUP 3.—*Meningiomas Arising from the Olfactory Groove.*—There were 5 examples of tumor in this region in this series, and in 1 of

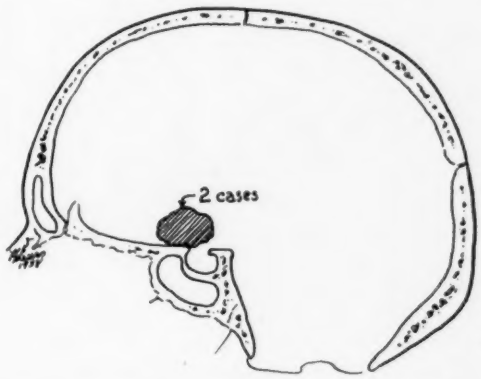


Fig. 8.—Schematic drawing to show the situation and relatively small size of suprasellar tumors (group 2).

these the patient died. As a rule, meningiomas in this region are the largest with which one has to deal, probably because their growth is slow and the symptoms of intracranial trouble are insidious. They start in the frontal fossa on one side and gradually push upward under the corresponding frontal lobe (fig. 9). The olfactory nerve on the side of the lesion has its function destroyed by direct pressure. Finally, the tumor grows laterally across the median line to the opposite side, under the other frontal lobe, and as this is compressed mental symptoms become progressively apparent (fig. 10). Eventually, signs of increased intracranial pressure appear. From the aforementioned changes it will be seen why the symptom complex described by Kennedy is pathognomonic for a lesion in this situation. This syndrome comprises:

(1) loss of the sense of smell on one or both sides; (2) optic atrophy on the side on which the tumor started (because of direct compression on the nerve); (3) choked disk on the opposite side (due to general

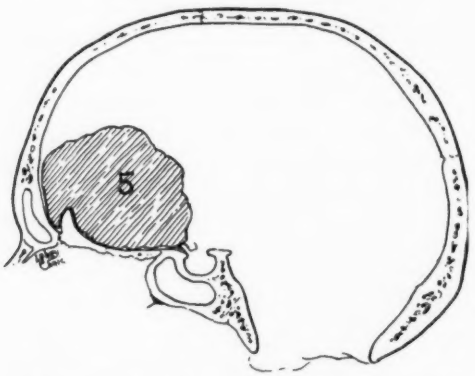


Fig. 9.—Site and large size of tumors arising from the olfactory groove (group 3).

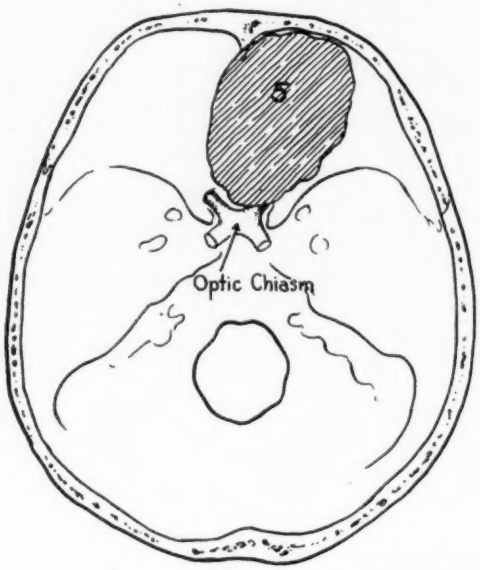


Fig. 10.—Basilar view of a meningioma arising from the olfactory groove, showing direct compression of the right optic nerve and extension of the tumor across the median line.

increased intracranial pressure), and (4) mental symptoms, such as failing memory, obtundity, indifference, changes in personality and untidiness.

In all cases of a meningioma arising from the olfactory groove operation has been in two or more stages. The clinical result of removal is as striking as it is satisfactory. The patients return to their normal personality, habits and work; unless vision has been impaired by long pressure of the tumor, they have no difficulty except from absence of the olfactory sense. My operative approach is always by a right frontal craniotomy, no matter which side harbors the larger portion of the

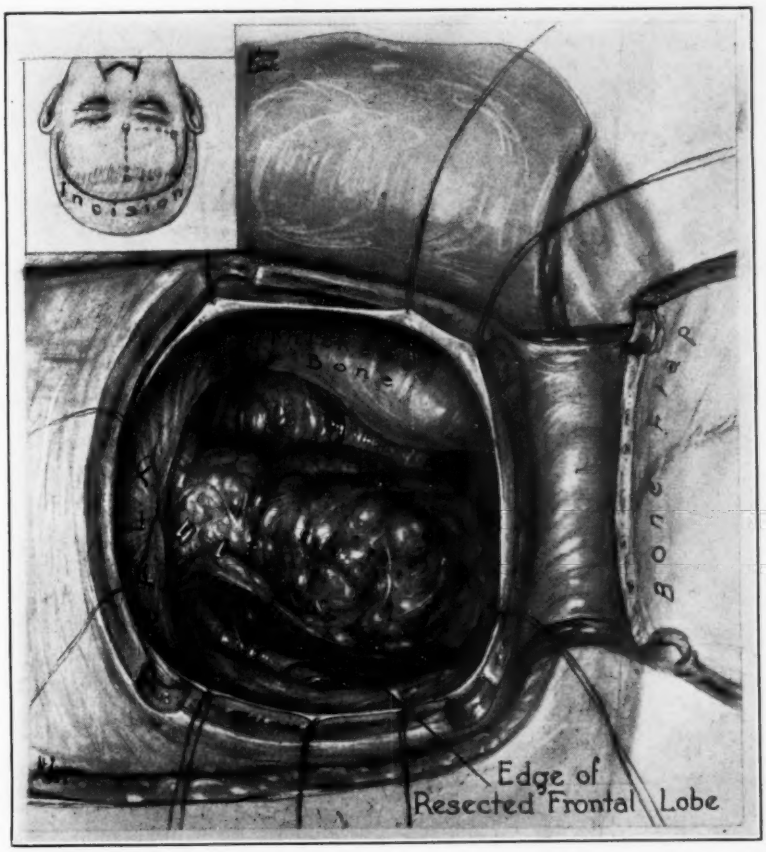


Fig. 11.—Operative sketch of exposure by right frontal craniotomy for removal of a recurrent meningioma arising from the olfactory groove. The tip of the right frontal lobe has been resected, exposing the growth, which extends under the falx to the left side. The thickened bone at the base anteriorly contains tumor cells and must be removed. The inset shows a "coronal" incision in the scalp within the hair line to prevent scar. The scalp is retracted forward and the bone flap turned down to the right side.

growth. The tip of the right frontal lobe is resected and the tumor on that side removed (fig. 11). At a subsequent session or sessions, the

same bone flap is reflected, and the remaining growth under the left frontal lobe is gradually taken out piecemeal by working under the falx, which often has to be split upward to gain room.

Another point concerned in the diagnosis is the roentgenographic picture. There is often thickening along the floor of the frontal fossa, and in 1 of my patients there was marked calcification within the growth. Three of the 4 living patients have returned to their usual occupations, but the fourth was blind before undergoing operation.

Fig. 12.—Patient with a meningioma behind the right orbit, causing typical unilateral exophthalmos and depression of the eye.

Group 4.—*Orbitotemporal Meningiomas.*—This group is extremely interesting. There were 9 cases in this series, a larger proportion than ordinarily exists. Seven of the 9 cases have occurred in women. The outstanding objective feature is the marked and gradually increasing protrusion of one eye (fig. 12). This is caused by the enormous bony thickening of the orbital roof and of the bone lateral to and beneath the orbit in the region of the sphenoid ridge, together with invasion of the orbit posteriorly by tumor which has extended through the bone from its intracranial origin. The meningioma arises in the dura in the region of the lesser sphenoid wing and most often is of the flat, "plaque"

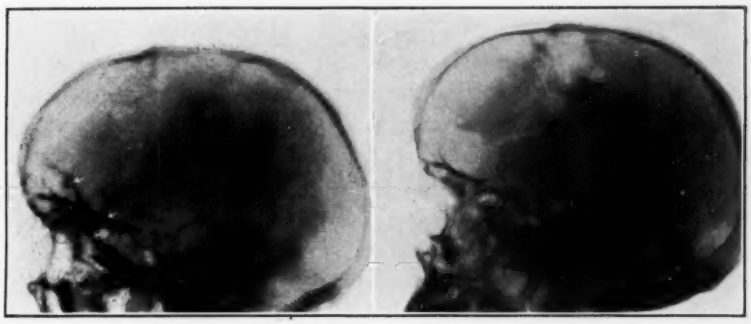


Fig. 13.—At the left, a roentgenogram of a patient with an orbitotemporal meningioma, showing enormous thickening of the bone above and posterior to the orbit. At the right, a roentgenogram of the same patient after operation, showing extensive removal of the area of bone involved by tumor.

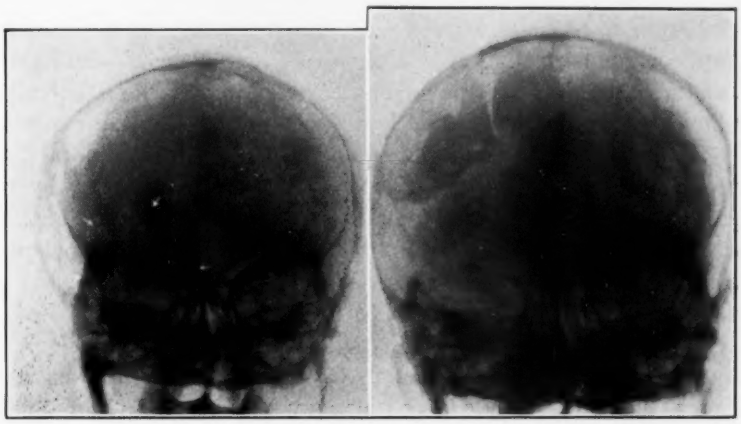


Fig. 14.—Anteroposterior roentgenograms in the same case as that illustrated in figure 13, showing, on the left, preoperative appearance of the bone and, on the right, appearance after removal. Note on the right the bone graft replacing the supraorbital ridge, which was involved by tumor.

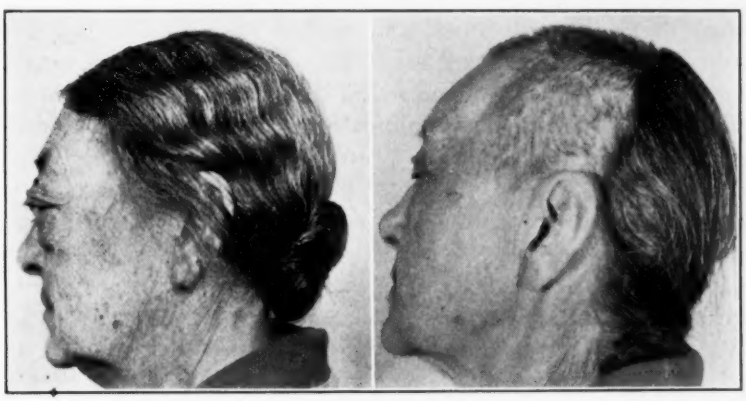


Fig. 15.—Photographs of a patient before and after operation, showing recession of the eyeball on the side of exophthalmos.

variety, its intradural portion being relatively insignificant so far as intracranial symptoms are concerned. These particular meningiomas, however, have an astounding faculty for invading and thickening the bone in their neighborhood, and it is the tremendous proliferation of bone together with the presence of tumor cells in the bone that causes the protrusion of the eye as well as prominence of the bone in the temporal region and occasionally along the supraorbital ridge. At times there is sufficient intracranial pressure to cause choked disks, but the main features are the unilateral exophthalmos and the enormous bony changes shown in the roentgenogram (fig. 13).

The surgical attack on meningiomas in this group is long and tedious. A frontal craniotomy is performed, after which the whole area of greatly thickened bone forming the roof of the orbit, as well as its lateral wall, must be gradually dug out by the use of an electrically driven burr and rongeurs and occasionally a mallet and chisel. This excavation should extend down to the optic foramen and laterally to the limits of the tumor-involved bone (fig. 14). After the removal of bone has been completed, the dura is opened and the intradural tumor removed. The intradural portion may be represented merely by what appears to be a thickened dural membrane, or it may be a sizable growth. The final step is to open the orbital capsule and allow the contents to bulge backward, in order to allow the eyeball to recede (fig. 15). If there is tumor within the posterior part of the orbit, it should, of course, be removed. One of my 9 patients succumbed to pneumococcic meningitis, as the tumor invaded the frontal sinus and the latter was widely opened. The others made excellent recoveries and are back at their usual occupations.

GROUP 5.—*Meningiomas Straddling the Sagittal Sinus and Spreading Laterally over Both Cerebral Hemispheres.*—Four patients in this series had tumors of this character. In 3 the tumors recurred after operations from seven to nine years previously. The most marked clinical feature in cases of these tumors is the great dome-shaped, tumor-involved growth of bone over the vertex of the skull, usually somewhat anterior (fig. 16). The tumor within the skull is flat. It invades the sagittal sinus usually for a considerable distance and spreads out over the surface of each cerebral hemisphere (fig. 17). Clinical signs include weakness and spasticity of the limbs opposite the side of greatest cortical compression, since these growths tend to be larger on one side of the sinus than on the other. Eventually, however, both sides, especially the legs, are involved if the tumor is not removed or if recurrence takes place after incomplete removal.

At operation a large skin flap must be turned back over the great cranial hyperostosis and the latter removed widely, since it is involved

with tumor cells (fig. 18). The dura is incised along the outer margins of the tumor on either side of the sagittal sinus, the incisions being carried up to the sinus anteriorly and posteriorly. The sinus is then

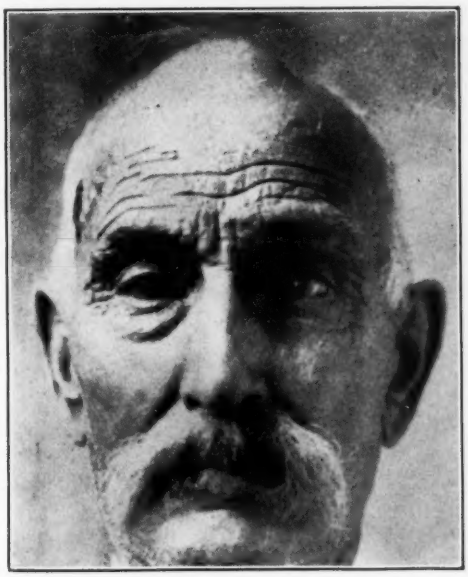


Fig. 16.—Characteristic prominence in the skull overlying a meningioma which straddled the longitudinal sinus (reproduced from my article: Surgery of the Brain, Nelson Loose-Leaf Living Surgery, vol. 2, p. 400). This patient was not in the present series.

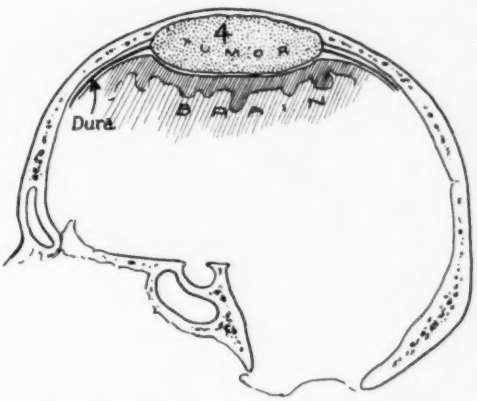


Fig. 17.—Schematic representation of a meningioma of group 5.

ligated with silk ligatures beyond its point of invasion by tumor, and the whole block is removed by finally incising the falx below the sinus.

I have removed with tumor in this manner from 5 to 12 cm. of the sagittal sinus anterior to the rolandic area (fig. 19). All the patients in this group are living, but 2 are considerably incapacitated by weakness of one or the other leg.

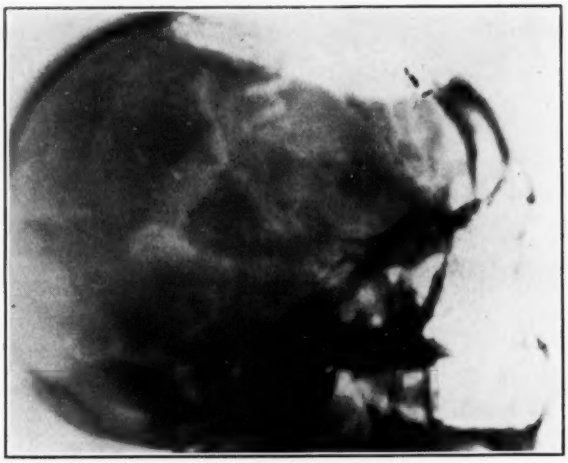


Fig. 18.—Area of removal of bone over the cranial vault in a case of a meningioma straddling the longitudinal sinus.

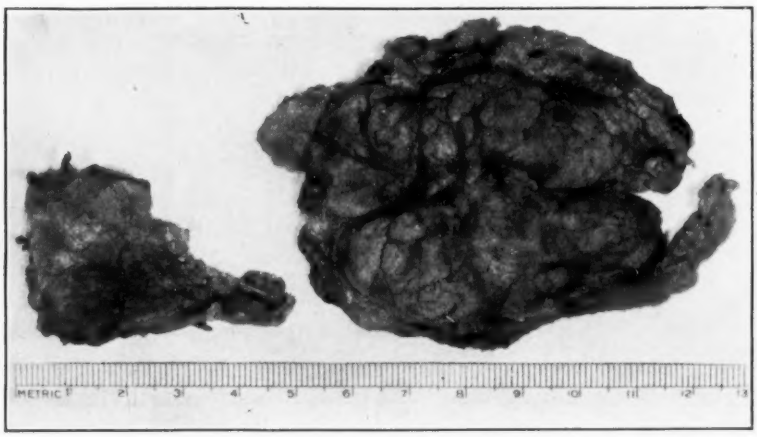


Fig. 19.—Specimen of a tumor of group 5, removed with the tumor-invaded sinus.

GROUP 6.—*Meningiomas, Often Bilateral, Arising from the Falx and Growing Laterally and Largely Subcortically.*—It is not necessary to dwell on this group in detail, but it should be mentioned that a tumor

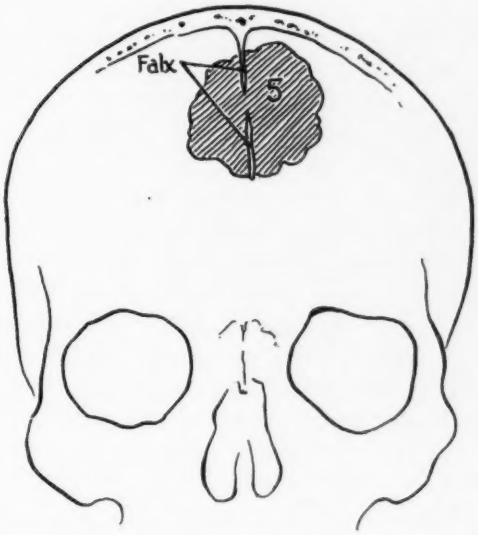


Fig. 20.—Diagrammatic illustration of meningiomas arising from the falx and extending bilaterally.

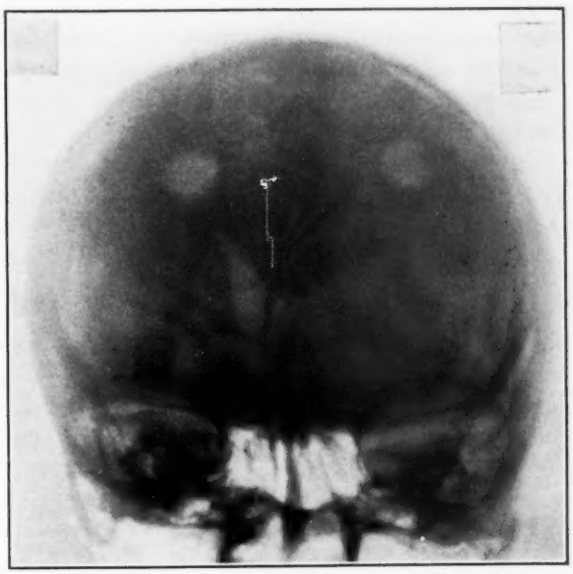


Fig. 21.—Ventriculogram of a meningioma arising from the falx. The left ventricle is pushed downward, and both ventricles are displaced to the right.

in this situation is extremely difficult to approach and remove successfully. Growths of this type have been among the most highly vascular in my series, and their attachment all the way down the falx, from the sagittal sinus to the inferior border, makes their mobilization excessively hard. In 2 instances the tumor extended through the falx to compress the opposite hemisphere (fig. 20). Five patients had tumors belonging in this group, 2 of whom died, 1 after a first stage procedure without an attempt to remove the tumor. In all cases ventriculographic examination was required, since roentgenographic and other localizing features were absent. The characteristic ventriculographic finding is shown in figure 21.

GROUP 7.—*Multiple Meningiomas.*—There were 4 patients with multiple tumors. Two of these underwent a radical operation, and 1 died. The other 2 died, both of sudden respiratory failure, 1 after ventriculographic examination and 1 after the first stage of attempted exploration. The 1 living patient is able to carry on her housework, but is subject to epileptiform attacks.

GROUP 8.—*Meningiomas in Various Locations.*—The remaining patients harbored meningiomas in unusual situations. One had a large growth in the region of the pineal body, compressing the corpora quadrigemina, which was successfully removed by preliminary radical resection of the right occipital lobe. In another case the tumor was within the left lateral ventricle and was likewise removed successfully, the patient now being well except for minor paraphasic difficulties. A third patient had an extremely vascular growth arising from the sheath of the gasserian ganglion. She succumbed shortly after the operation, probably owing to shock.

Four patients had meningiomas of the posterior fossa and showed symptoms of cerebellar compression. One of these died of pneumococcic meningitis, since the growth involved the middle ear, but the others recovered except for slight residual ataxia.

GENERAL CONSIDERATIONS, INCIDENCE AND MORTALITY

In a review of the group as a whole, several features of interest have been emphasized. The 60 cases of meningioma which form the present material occurred in a series of 315 cases of histologically verified tumors of the brain. Thus, they represent 19 per cent of all the intracranial growths at this clinic, a somewhat larger figure than that given for most series. Cushing's figure in a series of 2,000 verified tumors of the brain of all types was 13.4 per cent. My higher percentage may mean that more meningiomas are being verified with the increasing use of ventriculography, but it is likely that many factors come into play. If this high percentage persists it will have favorable results, for meningiomas as a rule are potentially capable of complete removal.

Two other facts are of interest: Forty-six of the 60 cases of meningioma (76.6 per cent) occurred in women, and in 38 of the 56 cases, or 68 per cent, in which the tumor was not multiple the location was in the anterior half of the brain. The latter point was likewise brought out by Frazier and Alpers, as mentioned previously. The predominance in women is at variance with Dandy's experience. He stated that in his cases males predominated.[7]

In the discussion of the various types of meningioma, reference has been made to the number of deaths occurring in each group. In summary, it should be said that 10 of the 60 patients died in the hospital, a mortality rate of 16.6 per cent. One of the patients died after a ventriculographic examination, having refused further operation; the real case mortality, therefore, is 15 per cent. The 60 patients were subjected to seventy-nine major operations, exclusive of reelevations for removal of postoperative clots, drainage and so forth; thus, what has been termed the operative mortality is 12.6 per cent.

---

7. Dandy, W. E., in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12.

Case Reports

TREATMENT OF ENCAPSULATED ABSCESS OF THE BRAIN

Visualization by Colloidal Thorium Dioxide

EDGAR A. KAHN, M.D., ANN ARBOR, MICH.

It is well known to surgeons that the deeper an abscess lies the more technically difficult is its successful drainage. This applies especially to abscess of the brain.

At a meeting of the American Medical Association on May 13, 1936, I presented a method [1] by which a deep-seated encapsulated abscess may be forced to migrate to or above the surface of the cranial vault by utilization of the increased intracranial pressure. The method consists, briefly, in palpation of the wall of the abscess through a trephine opening, a dull cannula being used. A decompression is made over what is thought to be the most superficial surface of the abscess, and the abscess is excised or drained on its appearance at the surface several days later.

Since this communication my colleagues and I have had occasion to visualize directly a deep-seated abscess of the temporal lobe by means of a contrast medium, colloidal thorium dioxide (thorotrast). A series of roentgenograms taken after evacuation of the abscess and instillation of colloidal thorium dioxide graphically shows the migration of the abscess to the surface, followed by its spontaneous extrusion (fig. 1). The fact that colloidal thorium dioxide is phagocytosed by cellular elements of the capsule makes its instillation an adjunct to any form of treatment for abscess of the brain.

REPORT OF CASE

V. C., a boy aged 12, was admitted to the University Hospital on the night of Dec. 30, 1937. He had been well until October 15, when he had a severe attack of scarlet fever. On November 15 bilateral otitis media developed, with spontaneous rupture of both tympanic membranes, and three days later the boy became totally deaf. Bilateral mastoiditis soon became evident, but because of the patient's poor condition operation was deferred until December 5. At this time a large, necrotic mastoid was found on the left. The sinus was exposed in this region. On the right also the sinus was exposed, as was the dura over the temporosphenoidal lobe. There were purulent granulations over the dura in this area.

One week later (December 12) signs of meningism suddenly appeared. A spinal puncture revealed a count of 260 white blood cells per cubic millimeter. (It

---

From the Department of Surgery of the University of Michigan Medical School, the clinic of Dr. Max M. Peet.

1. Kahn, E. A.: The Treatment of Encapsulated Brain Abscess, J. A. M. A. **108**:87 (Jan. 9) 1937.

was undoubtedly at this time that the intracranial complication developed.) The symptoms cleared up after three days, and the boy was comparatively well until December 28, when photophobia developed, accompanied by frontal headache on the right side and by nausea and vomiting. Two days later the patient was admitted to the University Hospital.

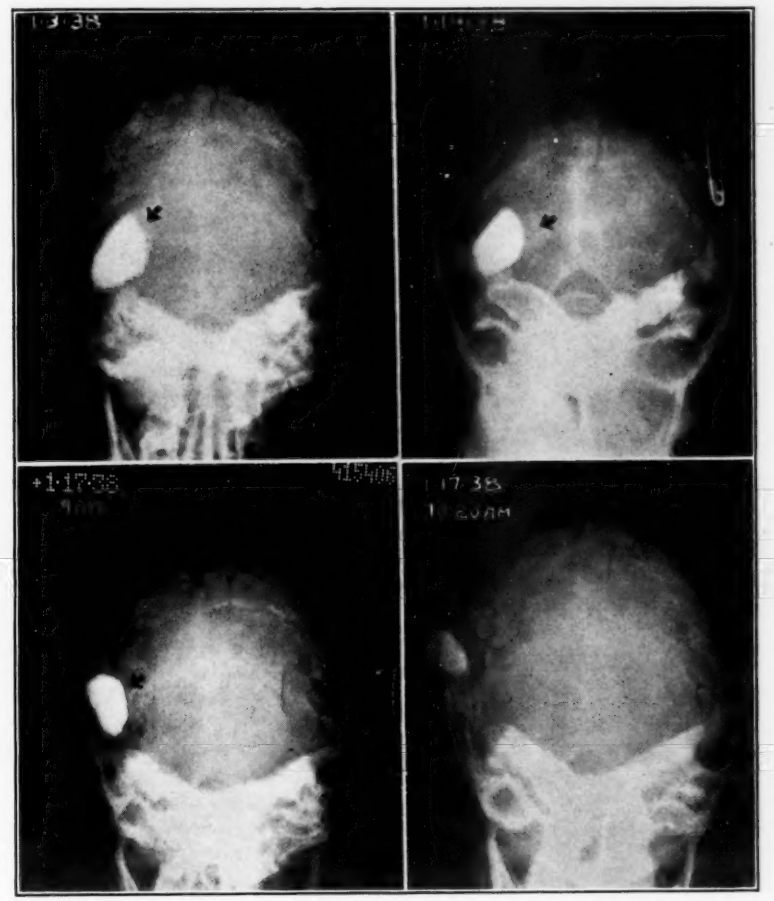


Fig. 1.—Migration and extrusion of a deep-seated abscess. The first roentgenogram was taken seventy-two hours after the instillation of colloidal thorium dioxide. The arrow points to the capsule, which was well shown on the original films.

Examination.—The boy was poorly nourished and extremely ill. He was stuporous but was capable of being aroused by strong stimuli. Well healed scars from a recent mastoidectomy were seen. There was perforation of both tympanic membranes, with a slight mucopurulent discharge. There was moderate stiffness of the neck, and Kernig's sign was present bilaterally. Papilledema of 1.5 D. without hemorrhages or exudate was noted. Slight central paralysis of the left

side of the face was demonstrable. There was complete bilateral deafness. The deep tendon reflexes were slightly increased on the left and suggestively strong on the right. The leukocyte count was 14,600 per cubic millimeter.

Course.—A diagnosis of abscess of the right temporal lobe was made. On the morning after the boy's admission a trephine opening was made in the right temporal region. The incision was placed higher than usual because of the previous mastoidectomy incision. The abscess capsule was palpated at a depth of 4.5 cm. from the surface of the brain. It felt only slightly firmer than is characteristic of the normal ventricular wall. About 1 ounce (30 cc.) of pus was evacuated under great pressure, its evacuation apparently emptying the cavity.

Because of the patient's poor condition and because of the thinness of the capsule it was decided that no further operative procedure should be attempted at this time. Accordingly, about 6 cc. of colloidal thorium dioxide was instilled into the abscess cavity. The needle was withdrawn and the incision closed.

Roentgenograms revealed the colloidal thorium dioxide to be encapsulated deep in the temporal lobe. The shape of the mass was somewhat irregular, suggesting that the abscess had almost completely collapsed after drainage of the pus.

The improvement in the symptoms was rapid, and within four or five days the patient seemed almost normal. Sulfanilamide was given for a few days but was soon discontinued. Culture of the pus revealed Streptococcus haemolyticus.

Roentgen studies on Jan. 3, 1938, showed evidence of increase in the size of the abscess. The thin wall of the capsule could now be distinctly seen rising above the main mass of the colloidal thorium dioxide. (This proves that colloidal thorium dioxide is sufficiently taken up by the capsule of an abscess of the brain to make the lesion radio-opaque within seventy-two hours.)

Nausea and vomiting recurred on January 13. The boy became lethargic and complained of frontal headache and blurring of vision. A roentgenogram (fig. 2) revealed a definite ballooning of the eggshell-like capsule above the main mass of colloidal thorium dioxide.

With the patient under nitrogen monoxide–oxygen anesthesia a vertical incision was made, starting from the lowest point of the previous incision. The temporal muscle was split and retracted. An area of bone about the size of a half-dollar was removed from the temporal squama just below the previous trephine opening. The dura was opened in a stellate manner and the blood vessels on the surface of the brain coagulated. There was considerable increase in intracranial pressure. An iodoform pack was placed over the brain substance to insure firm adhesion to the dura.

On the following day the patient was ill, with nausea and vomiting. The rectal temperature rose to 101 F. On the next day the boy was still nauseated and complained of pain in the incision. On January 16 hemorrhages were noted for the first time in the right fundus.

At 9:00 a. m. on January 17 a roentgenogram (fig. 3) was taken, which showed that the abscess had migrated until it lay directly against the osseous defect. Because several films were not perfectly satisfactory from a technical standpoint, several new films were taken at 10:20 a. m. After this procedure the patient was sent to the operating rooms for drainage of the abscess. Since the first set of films was excellent from a localizing standpoint and since nothing had been done to the patient during the hour and twenty minutes which elapsed between the taking of the two sets of films, it did not occur to the operator to look at the second set. This was the cause of the confusion which followed.

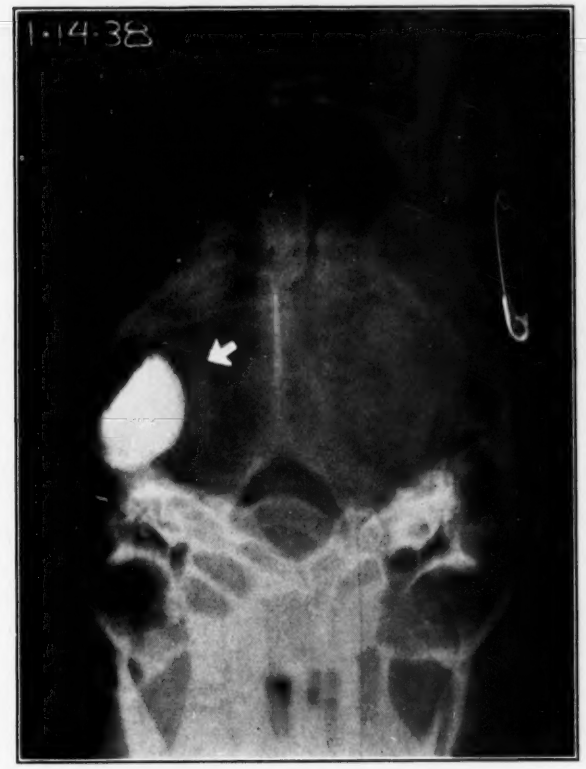


Fig. 2.—Detail of a roentgenogram, showing the capsule of the abscess.

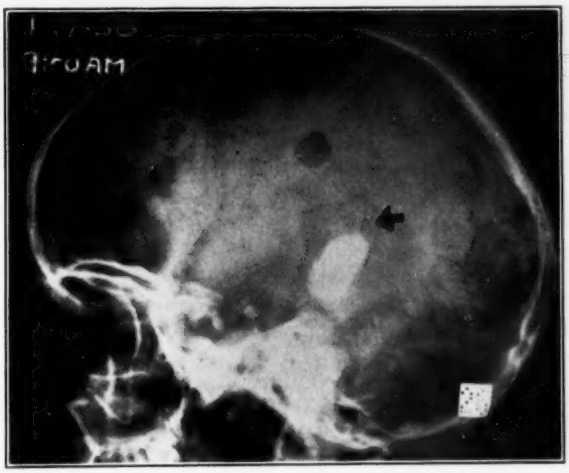


Fig. 3.—Lateral view, showing the capsule of the abscess at the margin of the bone defect.

Nitrogen monoxide–oxygen anesthesia was induced just after 11:00 a. m. The herniation was seen to extend outward for about 1 inch (2.5 cm.) from the defect in the skull. The surface vessels were completely thrombosed. Removal of the brain substance was commenced by suction. After less than ¼ inch (0.6 cm.) had been removed it was seen that the abscess capsule, which only shortly before had been known to lie within the cranial vault, had now been extruded. This was extremely perplexing.

The capsule was traced downward, little pus being seen, and before the operator realized it the entire abscess had been removed. The abscess had apparently ruptured just after extrusion. (It had previously been planned merely to cut off the dome of the abscess, as suggested to me by King [2] and then stitch

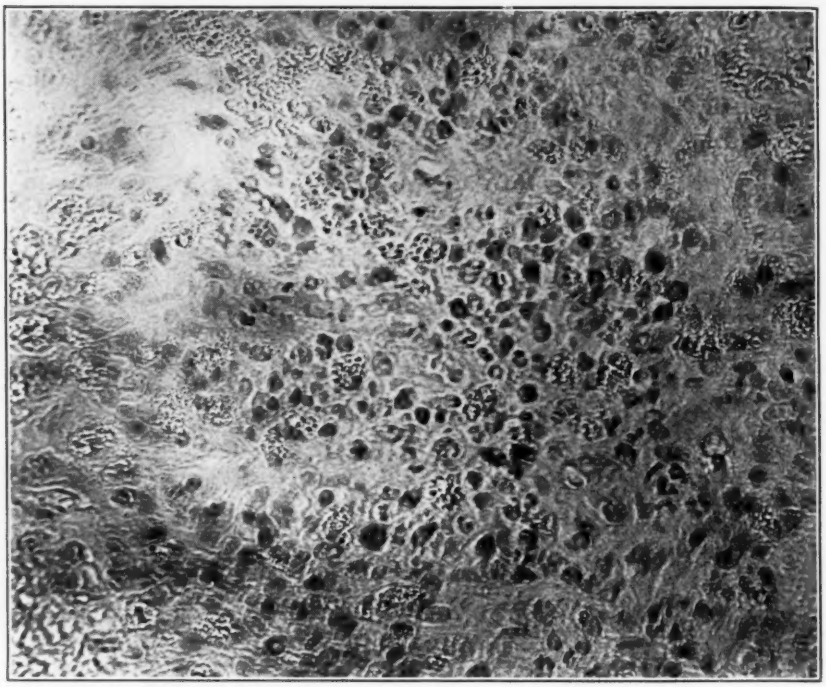


Fig. 4.—Photomicrograph of the abscess wall, showing the phagocytosed particles of colloidal thorium dioxide. The section is thrown slightly out of focus to demonstrate the refractile cell inclusions.

the capsule to the galea after the method of Horrax.[3]) A small stalk running down toward the petrous bone was also excised. The entire procedure resulted in an edematous, raw brain surface presenting at the cranial defect; this the operator would have preferred to avoid. A pack of metaphen in oil was placed over the defect and the scalp loosely sutured around it.

Convalescence was somewhat stormy for several days, the maximum rectal temperature being 103 F. Photophobia and some stiffness of the neck were present for two days. There was some watery discharge for several days, but it

2. King, J. E. J.: Personal communication to the author.

3. Horrax, G.: A Method for the Treatment of Certain Chronic Encapsulated Brain Abscesses, S. Clin. North America **14**:1179 (Oct.) 1934.

was thought to be transudation from the exposed brain substance. A small amount of sulfanilamide was given. On the sixth postoperative day the temperature had returned to normal and the boy was free from symptoms. There were some separation of the wound and herniation of the granulating brain surface. The latter was easily controlled by lumbar puncture.

A partial secondary closure was performed on February 14. Visual fields taken on February 24 showed almost complete homonymous hemianopia with splitting of the macula. The papilledema was receding, but the disks were not yet flat.

The patient was discharged on February 27, feeling entirely well. A small granulating area was still present.

Histologic Study.—The report on the pathologic material by Dr. C. V. Weller was as follows:

This material consists of portions of the wall of a cerebral abscess. The chronicity of the process is made evident by the extensive connective tissue proliferation as well as glial proliferation resulting in encapsulation. The abscess is lined by vascular pyogenic granulation tissue in which there are numerous polymorphonuclear leukocytes. In addition to the usual features of a chronic abscess of the brain, the granulation tissue lining the cavity contains many large mononuclear phagocytes packed with small, glistening granules. These are pale yellow by transmitted light. Since they have a refractive index unlike that of any other substance in the section, they present a brilliant luster as they pass in and out of focus. Phagocytes containing this material occur closely grouped to a depth of about 1.5 mm. in the granulation tissue. Since this material is not usually found in the granulation tissue of an abscess of the brain and since colloidal thorium dioxide is known to have been introduced into this one, there can be little doubt that the material in question is phagocytosed colloidal thorium dioxide. Moreover, it agrees in every particular with previous observations on colloidal thorium dioxide after being taken up by phagocytes.

HISTORICAL NOTE

Freeman and Schoenfeld [4] in a discussion of the intraventricular use of colloidal thorium dioxide suggested its use in cases of abscess of the brain to determine the extent of the cavity and the state of encapsulation. This was tried by them in 1 case, in which a small amount of pus appeared in the needle on attempted ventricular puncture. Three cubic centimeters of colloidal thorium [5] dioxide was injected. Roentgenograms showed so diffuse a shadow that I do not believe the abscess was encapsulated. The patient, who was moribund at the time, died a few hours later, and permission for autopsy was not obtained.

TECHNIC

The technic is similar to that previously described by me,[1] except that colloidal thorium dioxide is injected into the abscess when the exploratory trephine opening is made.

4. Freeman, W., and Schoenfeld, H. H.: Ventriculography with the Use of Colloidal Thorium Dioxide, Arch. Neurol. & Psychiat. **36**:907 (Oct.) 1936.

5. Freeman, W., and Schoenfeld, H. H.: Personal communication to the author.

In my opinion the following is the best procedure: A trephine opening is made over the suspected area. If the rubbery resistance characteristic of abscess of the brain is met with, the dull exploring cannula is plunged into the cavity. The pus is evacuated and about 6 cc. of colloidal thorium dioxide instilled. If the capsule is not thought to be sufficiently firm, one should wait several weeks before proceeding, tapping the abscess again if necessary. Roentgenograms should be taken at various times during this period.

If the capsule is thought to be sufficiently firm to hold sutures, an opening about the size of a half-dollar is made in the bone directly over the most superficial part of the abscess as visualized by roentgen studies. The dura is opened in a stellate manner. The surface vessels are coagulated and the arachnoid membrane sealed to the cortex at the margin of the wound. An iodoform pack is placed to further the formation of adhesions, completely sealing off the subdural and subarachnoid spaces at the margins of the defect.

In from three to seven days the capsule will have arisen to or above the surface of the skull. (This has occurred in my own 5 cases, in all of which the patients recovered. In none of them, however, was the abscess completely evacuated of pus at the time the decompression was made. It is possible that evacuation at this time would retard the migration of the abscess to the surface. Roentgen study would, of course, determine this.) The edematous brain substance is now removed by suction, the dome of the abscess being widely exposed. The dome is then excised and the capsule sutured to the galea as described by Horrax.[3] This provides a barrier to prevent excessive exposure of edematous brain substance. It is undoubtedly safer than the more radical excision of the capsule performed in 3 of my 5 cases.

The mistake made in the case described was in not realizing that the abscess had been extruded. The safest procedure would have been to open the abscess wide, excise the dome and place a pack within the now comparatively shallow cavity.

SUMMARY

The advantages of using a contrast medium (colloidal thorium dioxide) in the treatment of encapsulated abscess of the brain are:

1. The abscess is visualized directly. McKenzie[6] has logically advised that when an abscess oblique to the exploring needle is encountered a new opening should be made over what is mentally pictured as the most superficial part of the abscess. It is obvious that an abscess visualized directly by a contrast medium can be most accurately attacked at its most superficial point.

2. The colloidal thorium dioxide particles are phagocytosed by cellular elements of the capsule, so that increase in size of the abscess is demonstrable, even though the pus and the contrast medium do not mix freely.

6. McKenzie, K. G.: The Treatment of Abscess of the Brain, Arch. Surg. **18**:1594 (April) 1929.

3. At the time of drainage the abscess sometimes collapses so that the capsule becomes "lost" in the depth of the brain substance. This frequent and disastrous complication could be minimized if the capsule were radio-opaque.

4. In the method of Clovis Vincent,[7] in which one waits long periods before excision of the abscess by open operation, there would be distinct advantage in constant visualization of the abscess.

5. A method has been advocated by Dandy [8] whereby the abscess is treated by repeated tappings.. A clue would be had as to the proper time for subsequent tappings, which could be done under fluoroscopic control if colloidal thorium dioxide were instilled at the first drainage. The phagocytosis of the contrast medium by cellular elements of the capsule would be of advantage in such therapy.

Since comparatively small amounts of colloidal thorium dioxide are used and since this is almost entirely removed, there seem to be no disadvantages in the use of the method.

---

7. Vincent, C.: Sur une méthode de traitement des abcès subaigus des hémisphères cérébraux; large décompression, puis ablation en masse sans drainage, Gaz. méd. de France **43**:93 (Feb. 1) 1936.

8. Dandy, W. E.: Treatment of Chronic Abscess of the Brain by Tapping: Preliminary Note, J. A. M. A. **87**:1477 (Oct. 30) 1926.

CHRONIC PERIVASCULAR DEMYELINATION (HOMOPHASIC CEREBROSPINAL DEMYELINATING PERIANGIOSIS)

GABRIEL STEINER, M.D., DETROIT
Research Professor of Neurology and Neuropathology

Focal areas of demyelination, with or without degeneration of axons, are a common observation in a variety of diseases of the central nervous system and in many experimentally produced conditions. There are the circumscribed cortical lesions of dementia paralytica; the lesions described in bacillary dysentery (Spielmeyer [1]) and those in encephalitis following measles (Walthard,[2] Ferraro and Scheffer [3] and Putnam [4]), varicella (van Bogaert [5]) and variola (Brouwer [6]). There are the pathologic changes resulting from burns (Globus and Bender [7]) and carbon monoxide poisoning (doubtful case reported by Hilpert [8]). It is obviously a mistake to conclude that every case in which there are disseminated circumscribed areas of demyelination must be an instance of multiple sclerosis. The pathologic diagnosis depends not only on the histologic picture of the individual lesion but on its position and total distribution. In other words, if one adds to the "histotypical"

From the Department of Pathology, the Wayne University College of Medicine.

1. Spielmeyer, W.: Infektion und Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161, 1930.

2. Walthard, K. M.: Spätstadium einer Encephalitis nach Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:176, 1930.

3. Ferraro, A., and Scheffer, I. H.: Encephalitis and Encephalomyelitis in Measles: A Pathologic Report of Six Cases, Arch. Neurol. & Psychiat. **25**: 748 (April) 1931.

4. Putnam, T. J.: Studies in Multiple Sclerosis: VIII. Etiologic Factors in Multiple Sclerosis, Ann. Int. Med. **9**:854, 1936.

5. van Bogaert, L.: Contribution clinique et anatomique à l'étude des manifestations neurologiques et psychiatriques de l'infection varicelleuse, J. de neurol. et de psychiat. **30**:623, 1930; Histopathologische Studie über die Encephalitis nach Windpoken (Encephalitis postvaricellosa), Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:201, 1932.

6. Brouwer, B.: Ueber Myelitis bei Pocken, Zentralbl. f. d. ges. Neurol. u. Psychiat. **61**:484, 1931.

7. Globus, J. H., and Bender, M. B.: Disseminated Toxic Degenerative Encephalopathy (Disseminated Sclerosing Demyelination) Secondary to Extensive and Severe Burns, J. Nerv. & Ment. Dis. **83**:518, 1936.

8. Hilpert, P.: Kohlenoxydvergiftung und multiple Sklerose, Arch. f. Psychiat. **89**:117, 1929.

characteristics what may be called the "topotypical" features, multiple sclerosis is found to have a clearcut, characteristic anatomic picture.

Aside from this practical problem of classification, the question of demyelination merits consideration from the pathophysiologic standpoint. Here there is a great hiatus in knowledge. The myelin sheaths of the central nervous system undoubtedly are susceptible to injury, and I believe that present histologic methods are insufficient to detect slight alterations in them. Myelin is a lipoid, and one uses lipoid stains, such as hematoxylin, nile blue sulfate, scarlet red and sudan III, to bring it out. With these stains different pictures are observed at various stages of the same disease, and various shades of color are more or less typical of certain diseases (familial amaurotic idiocy, Merzbacher-Pelizaeus disease, Scholz's type of familial diffuse sclerosis). It is not known, however, what the chemical or chemicophysical nature of the substance so colored may be. The effect of various types of toxins on myelin sheaths in vitro was studied by a number of investigators (Brickner,[9] Weil and Cleveland [10] and others). It was thought that a blood lipase causes degeneration of the myelin sheaths, but that other agents can produce the same effect. Histopathologically, there are other points of interest. It is possible that there is not only a cellular but an acellular, perhaps a catalytic or fermentative mechanism for the breaking down of myelin. I [11] described such an acellular process in cases of dementia paralytica (*Myelopholiden,* or myelin refuse in focal areas of demyelination). Hallervorden and Spatz,[12] speculating on the pathogenesis of the concentric bands of demyelination in their case of "leukoencephalitis concentrica," suggested that a toxin may spread from the blood vessels by a mechanism similar to the formation of Liesegang's rings. It is significant that in cases of dementia paralytica and multiple sclerosis the lipoid reactions in the foci of demyelination in the gray matter seem to be different from those in the white matter. Compound granule cells are rare, and material stained with sudan III or scarlet red is scarce in the gray matter.

The following case bears on the question of demyelination in general and the differentiation between conditions showing disseminated circumscribed areas of demyelination and multiple sclerosis.

F. J. G. was born at Neustadt, Germany, on April 25, 1894. The family history was without significance. The patient's childhood and youth were apparently normal. He was an industrious, capable mechanic, who had not been ill previously. He was not exposed to heavy metal or other industrial intoxica-

9. Brickner, R. M.: Studies on the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **23**:715 (April) 1930.

10. Weil, A., and Cleveland, D. A.: A Serologic Study of Multiple Sclerosis, Arch. Neurol. & Psychiat. **27**:375 (Feb.) 1932.

11. Steiner, G.: Krankheitserreger und Gewebsbefund bei progressiver Paralyse (Pathogenese des herdförmigen Markscheidenzerfalls), Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:632, 1931.

12. Hallervorden, I., and Spatz, H.: Ueber die konzentrische Sklerose und die physikalisch-chemischen Faktoren bei der Ausbreitung von Entmarkungsprozessen, Arch. f. Psychiat. **98**:641, 1933.

tion. At the outbreak of the World War he was not drafted, being considered indispensable at his work. A year later, however, in 1915, he was drawn into service in the infantry. In August 1916 he was transferred to the aviation corps. During his service as an aviator he had many accidents, including nine forced landings and three "crack-ups." He was never rendered unconscious or seriously injured, however. He received hospital treatment only once during the war, for catarrhal urethritis. This was not gonococcic. He was free from syphilis.

The present illness began with a "feeling of nervousness" occasioned by flying and the resultant accidents. In August 1918 he was transferred from active service to a post as aviation instructor.

After the war was over, he was apparently no longer competent as a mechanic. He had to seek new jobs in 1922 and 1924 and was frequently unemployed. In August 1924 he began to work part time in a state customhouse. Since the end of the war he had been irritable, becoming angry over trifles. In 1924 he sought medical care for the first time. A neurologist made a diagnosis of "neurasthenia." In 1925 another neurologist diagnosed the condition as "cyclothymic depression."

First Admission to the Hospital.—The patient was admitted to the psychiatric and neurologic clinic at Heidelberg University on Dec. 8, 1926, with the complaint of attacks of forced laughter, which were almost always associated with an urge to suicide. He had become extraordinarily forgetful and had to make written notes of everything. He was overreactive emotionally. He cried easily and after the death of his mother, wept frequently. In attacks of rage he threatened to set his wife's bed afire. During a fit of anger he attempted to commit suicide by inhalation of gas. He suffered from constipation, frequent urination (approximately once an hour during the day), despite a small intake of fluid, and decrease in sexual potency.

Examination.—General examination, including that of the chest and abdomen, revealed nothing abnormal. Neurologic examination showed slight ptosis and exophthalmos on the left. Both optic nerves were markedly atrophied. The visual fields were diminished peripherally. There were bilateral scotomas for colors; visual acuity was 5/7.5 bilaterally. The pupillary and corneal reflexes were normal. The other cranial nerves showed no abnormalities. The arm reflexes were increased slightly and the Hoffmann reflex was sometimes elicited on the left. The abdominal reflexes were more active on the right than on the left. The cremasteric reflexes were active and equal; this was true also of the leg reflexes, although the Oppenheim reflex was occasionally present on the left. Sensation was normal. There was no intention tremor. No equilibratory disturbance was present in the lower extremities. Slight ataxia was present in walking, in the Romberg test and in standing on one leg. There were no spasms or rigor. Speech was occasionally slurred, with a slight tendency toward clinging to a sound or word (not scanning).

Psychiatric Examination: Concentration was moderately good. There was poor attention. The patient was unable to reproduce a column of four figures or to repeat three pairs of words. He was able to copy figures made up of two lines, but not of three (although as a mechanic he had formerly had a good deal to do with drawings). In looking at pictures he could grasp only details, without being able to take in the entire situation rapidly. For instance, when shown a carriage, he said: "Here is a horse and another horse and then a wagon, and a man is in it." He was poorly oriented as to place. There was marked emotional change: He was euphoric, tactless and uninhibited in the declaration of intimate, personal matters and yet shy and uncertain in his behavior. He had no

insight into the severity of his condition. During the examination he exhibited frequent outbursts of laughter, in spite of a marked effort at self-control.

Diagnosis.—The diagnosis was organic dementia, with the signs of a Korsakoff psychosis (poor attention and memory for recent events). The neurologic findings indicated cerebrospinal disease with many focal lesions. Since syphilis and epidemic encephalitis could be ruled out, a diagnosis of multiple sclerosis was probable.

Second Admission to the Hospital.—The patient was readmitted on May 11, 1928, having become progressively worse; in 1927 his condition was markedly poorer. On admission he was entirely unresponsive, remaining in bed all day. When he did get up he wandered about aimlessly. He performed no useful tasks, lost everything and had to be watched constantly. He had to be dressed and kept clean. He was very irritable. Gait was uncertain. His wife reported that for a year he had had frequent choking when eating.

The patient himself could furnish little information. He stated that he felt better and that his only difficulty was in walking. The forced laughter was less frequent; he no longer had suicidal thoughts and was not quarrelsome. He complained of severe constipation and frequent urinary incontinence.

Examination.—General physical examination gave normal results. The blood pressure was 118 systolic and 75 diastolic. The Wassermann reaction of the blood was negative. The urine was normal.

Neurologic Examination (signs that had appeared since the previous examination).—The left pupil was larger than the right. The left side of the mouth drooped. Speech was slurred, drawn out and slow. The abdominal and cremasteric reflexes were absent. The Hoffmann reflex was elicited, bilaterally. There were patellar clonus on the right and ankle clonus bilaterally. There was no Babinski or Oppenheim reflex. There was a suggestion of ataxia in the finger to nose and finger to finger tests. The gait was staggering even with the eyes open.

Psychiatric Examination: The patient did not remain in bed, even at night. He wandered about, could not become settled and talked to himself. He wet the bed and urinated on the floor once. He could not dress himself. He performed the simplest manipulations with great difficulty and slowness. Speech was slurred and difficult to understand; it was very rapid, with omission of entire syllables. He digressed and lost the thread of conversation. He was more disoriented as to place and markedly defective in calculation; attention was poor, and he showed severe loss of memory for recent events. He snatched everything that lay before him on the table. He spoke constantly, interrupting continually during the examination. He had no insight into his condition. He claimed that he could calculate excellently, could still speak perfect French and English and felt better and fresher than ever before. The emotional status was definitely euphoric.

Diagnosis.—The tentative diagnosis was severe, diffuse cerebral damage, probably multiple sclerosis. The condition was definitely worse. Intellectual disintegration was more advanced.

Third Admission to the Hospital.—The patient was admitted to the City Hospital of Ludwigshafen, Germany, on Sept. 2, 1928. The history was given by his wife. He repeated the same statements frequently during the same day. He was restless and always looking for something to do. The night before admission an epileptic seizure occurred, with grinding of the teeth and twitching of the arms and legs.

Examination and Course.—On admission he was comatose, with tonic and clonic contractions of the right arm and left leg. The Babinski sign was present on the left. There was marked spasticity of the right arm and leg. The abdominal reflexes were present. During the day there were repeated epileptic attacks, with muscular contractions chiefly in the right arm and left leg. The Wassermann reaction of the blood was negative. On the evening of September 4 there was a short convulsive seizure, with clonic contractions of the right arm and both legs; this recurred the following night. No further seizures occurred until his discharge in November.

Diagnosis.—The diagnosis was diffuse, severe cerebral disease, of uncertain origin.

Fourth Admission to the Hospital.—The patient was readmitted to the City Hospital, Ludwigshafen, on Dec. 29, 1930. There was then a sacral decubitus. Examination revealed ptosis of both upper eyelids and complete amaurosis (total optic atrophy). The abdominal and cremasteric reflexes could not be obtained. Ankle clonus, easily exhausted, was present on the right. There was a questionable Babinski sign on the left.

Clinical Diagnosis.—Multiple sclerosis, cerebral syphilis and encephalitis were considered.

The patient died on Jan. 7, 1931.

Autopsy Observations.—The costal cartilages were markedly ossified. There was edema of the lungs. Normal structures included the coronary arteries and the aorta and its large branches, which were comparatively free from arteriosclerosis.

The scalp and calvarium showed no abnormalities. The calvarium was easily separated from the dura, which was smooth and under normal tension. The inner surface of the dura was smooth and not adherent to the brain. The cerebrospinal fluid was somewhat increased. The brain weighed 1,160 Gm. It was small and somewhat atrophic, and the cerebral hemispheres were symmetric. The cerebral gyri showed no abnormalities, except that they may have been a little smaller than normal (fig. 1). The leptomeninges showed an unusual edematous type of thickening and were increasingly purplish red toward the frontal poles. There were delicate, pink fibrinous adhesions between the basal portions of the medial surfaces of the frontal lobes. The base of the skull did not exhibit any abnormal changes. The vessels at the base of the brain appeared delicate. The spinal dura did not show any abnormalities, nor were there any macroscopic lesions of the spinal cord.

The brain was fixed in solution of formaldehyde U. S. P. (1:10). Blocks were taken from the chief cortical areas, the basal ganglia, the cerebellum, the brain stem and the spinal cord. Hematoxylin and eosin; the Van Gieson stain; cresylviolet; phosphotungstic acid hematoxylin; sudan III and scarlet red; the Bielschowsky technic; the Cajal gold-mercury bichloride method; Van Gieson's stain and resorcin-fuchsin; the Biondi and Achucárro technic for mesenchymal fibers; the Gram, Levaditi and Steiner stains for spirochetes, the Weigert-Pal and Spielmeyer stains for myelin sheaths, and Spielmeyer's stain combined with sudan III were employed.

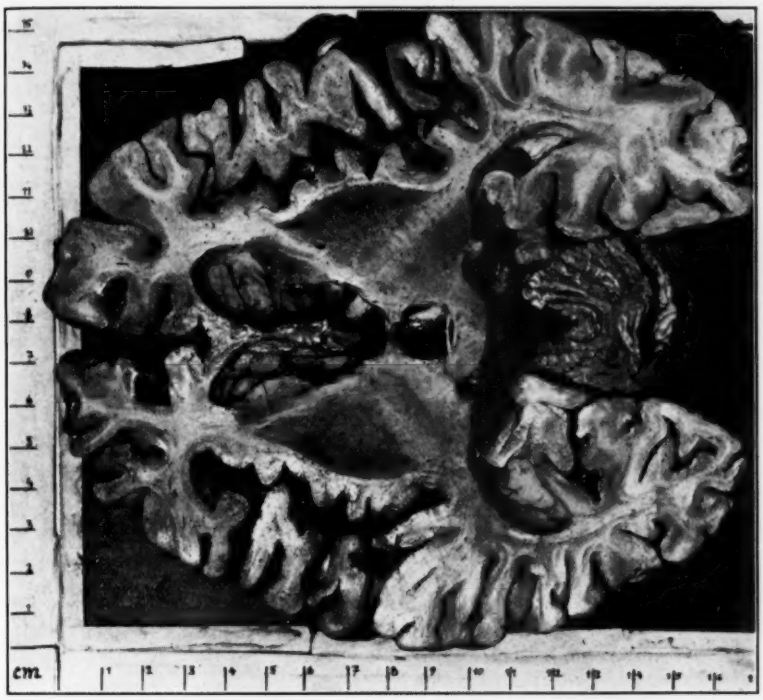


Fig. 1.—Horizontal section through the entire brain, showing hydrocephalus internus, narrowing of the convolutions and widening of the fissures.

Fig. 2.—Frozen section (Spielmeyer's stain for myelin sheaths) showing numerous small, irregularly scattered perivascular foci of demyelination. In the photograph, areas *a* and *b* correspond to figures 3 and 4, respectively.

Histologic Observations.—Meninges: In the pia-arachnoid, more numerous in the external portion of the subarachnoid space, were many erythrocytes unrelated to blood vessels. Monocytes containing hemosiderin, red blood cells or occasionally neutral fat were also present. The arachnoid villi appeared normal. The leptomeningeal vessels showed no abnormal changes in their walls, and none was occluded.

Cerebral Cortex: The gyri were smaller and the sulci wider than normal, owing to moderate cortical atrophy. There were numerous, irregularly scattered small foci of demyelination, varying relatively little in shape and ranging from the size of a pinpoint to 5 mm. in diameter (fig. 2). This produced a picture different from that seen in dementia paralytica, in which, owing to irregularity in size and

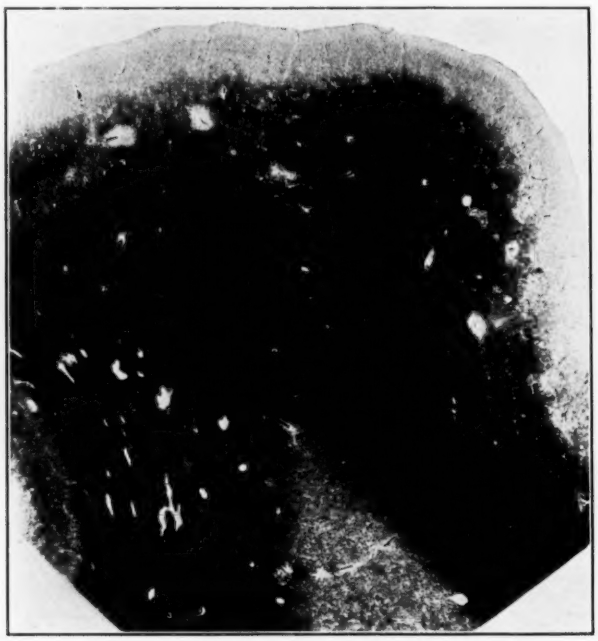


Fig. 3.—Area *a* in figure 2. Magnification, 7.75.

shape and to the confluence of lesions, the demyelination results in a "moth-eaten" appearance. In all layers of the cortex the demyelinated foci showed a definite and well marked relation to blood vessels. The cross section of a vessel was the central structure in circular demyelinated areas, and, similarly, a longitudinally cut vessel was observed in the cylindric or elongated oval lesions (figs. 3 and 4). Medium or small arteries and veins, but not capillaries, were involved. The upper cortical layers, down to the fourth, often contained wedge-shaped demyelinated areas (fig. 5). Small numbers of myelin sheaths of the tangential fibers were faintly or distinctly stained. The majority, however, had disappeared. In general, the cortical perivascular demyelination was not complete, particularly in the deeper layers. One or more myelin sheaths could be traced throughout each focus. The "punched-out" appearance of lesions often seen in other diseases, such as multiple

sclerosis or dementia paralytica, was encountered only rarely in this case. Most of the myelin sheaths, however, were sharply interrupted at the clearcut margin of a lesion. The ends of these sheaths usually showed no changes, except rare bulbous or cylindric swelling. Fragments of disintegrated myelin sheaths, like the *Myelopholiden* which I described [11] in cases of dementia paralytica, were lacking. No lipoid-laden phagocytes were present either in or about the demyelinated areas, except for a few in the adventitial spaces of blood vessels. These rare phagocytes were confined chiefly to the angles formed by branches arising from a vessel and were associated with small amounts of free fat. Abnormal lipoids were absent elsewhere.

Fig. 4.—Area *b* in figure 2. Magnification, 10.5.

The cytoarchitecture of the cortex was well preserved. Small foci of loss of ganglion cells were observed in all the layers and seemed to conform in shape and size to the demyelinated areas. They were more numerous, however, than the latter, and in the myelin sheath stains the ganglion cells in the demyelinated areas were seen to be well preserved. Since such focal loss of ganglion cells has been described in so-called normal brains, it is doubtful whether it can be considered as part of this particular pathologic picture. One observation, however, was somewhat in favor of its being a pertinent pathologic change. Some of the nerve cells surrounding the zones of cell loss were disoriented, their apical dendrites pointing toward the focus. This was more frequent and striking in the anterior

region of the cerebrum (frontal lobe) than posteriorly (occipital lobe). The rest of the ganglion cells appeared normal. The axis-cylinders in the demyelinated areas were well preserved. Their number may have been reduced, but this could not be definitely established. The area stained slightly lighter with the Bielschowsky stain, but this was true of most of the methods used (hematoxylin and eosin, phosphotungstic acid hematoxylin and the Van Gieson stain).

There was no reaction of the glia. Astrocytic proliferation was absent in the demyelinated areas and their surroundings, and there was no increase in glia fibers. The microglia and oligodendroglia cells were unchanged.

There were no pathologic changes in the walls of the blood vessels, and no inflammatory cells were present either in the perivascular spaces or in the surrounding parenchyma.

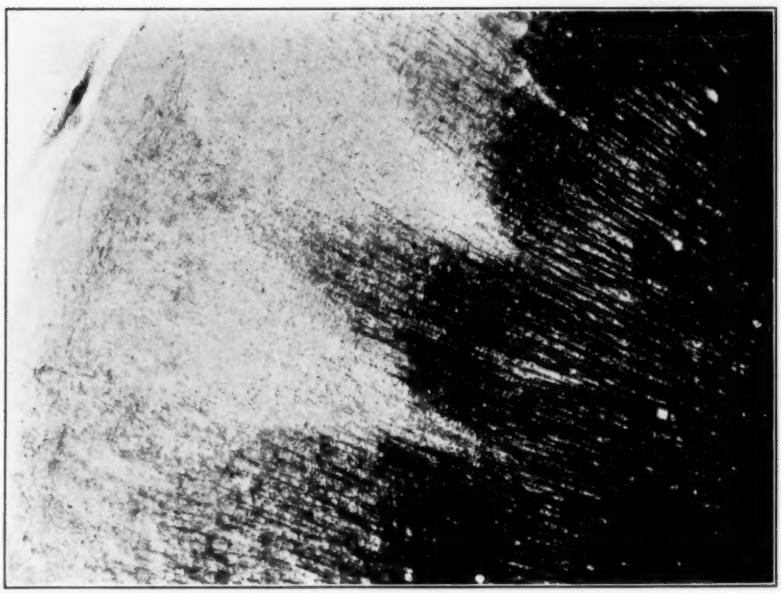


Fig. 5.—Wedge-shaped appearance of demyelinated areas. Magnification, 57.5.

The cortical areas of demyelination were equally frequent in the cerebral hemispheres. They were more numerous in the frontal and temporal lobes and the precentral and postcentral gyri and less so in the parietal and occipital lobes.

Cerebral White Matter: The subcortical white matter was reduced. It contained demyelinated areas similar in shape and size to those described in the cortex, but somewhat more regular. In the deeper portions of the white matter, the centrum ovale, the lesions showed only partial demyelination (*Markschatten-herde*). In these foci the myelin sheaths were complete, but stained more faintly than those outside the lesion. The periventricular portion of the white matter contained few demyelinated areas, considerably less than in the rest of the white matter. Phagocytes laden with lipoids were seen in the branching angles of vessels, as in the cortex, and seemed to be somewhat more numerous. Rarely, similar cells were seen in the parenchyma of the lesions. Phagocytes laden with hemosiderin were abundant in the adventitial spaces of the larger vessels. These were independent of the foci of demyelination and collections of lipoid. There

was no increase in astrocytes or their fibers in or about the demyelinated foci, and the microglia and oligodendroglia cells were unchanged. Occasional tortuosity of the blood vessels was noted.

Basal Ganglia: Similar demyelinated perivascular areas were observed in the caudate nucleus, putamen and globus pallidus. There was not loss of the large and small ganglion cells or any type of glial reaction.

Cerebellum: Small, strictly perivascular demyelinated zones, of the same size and shape as those seen elsewhere, were also present in the cerebellar white matter. They were less numerous in general than in the frontal lobes. They were most common in the white matter of the individual gyri. In the granular layer and in the deeper white matter they were less frequent. Often a lesion lay on the borderline between the white matter and the granular layer. In these foci demyelination was almost complete in the granular layer and only partial in the white matter. In the latter, demyelinated perivascular areas of the type of the *Markschattenherde* were the commonest lesions, totally demyelinated areas being rare. The molecular layer and the Purkinje cells showed no evident abnormality. Some of the blood vessels in the white matter were tortuous.

Brain Stem: Only a few demyelinated areas were seen in the gray and white matter. In the medulla, the intra-adventitial lipoid masses seemed larger than elsewhere, but were never present in the parenchyma. The external glial membrane was slightly thickened. Corpora amylacea were numerous here and in the subependymal region.

Optic Nerves: There was complete loss of myelin sheaths and axons in these nerves, with total replacement by dense isomorphous gliosis. In the peripheral zones hypertrophied astrocytes were present. There was no evidence of inflammation.

Spinal Cord: Few and small areas of perivascular demyelination were present in the cord. They were similar to those seen elsewhere. No secondary degeneration was present.

COMMENT

The most striking pathologic observation was that of focal areas of demyelination. These lesions differed from those in multiple sclerosis in that they were strictly perivascular. When a vessel was cut in cross section the area of demyelination was circular, with the blood vessel in the center; when the vessel was cut longitudinally the demyelinated zone was cylindric, with the blood vessel as its axis. The demyelinated areas in the cortex were occasionally wedge shaped, with the apex directed toward the white matter and the base toward the surface of the gray matter. The outer margin of the wedge was sometimes straight, rather than curved. The demyelinated areas were remarkably uniform in size. Large confluent lesions were absent. Occasionally, two small foci of demyelination lay side by side. These focal lesions, as has been pointed out, occurred throughout the central nervous system, in the gray as well as in the white matter, and their histologic character was similar throughout. They were demonstrable by every stain for myelin. With the Bielschowsky stain the presence of axis-cylinders in the demyelinated areas could be demonstrated. The observations of importance in differentiating these focal lesions from those in multiple sclerosis were: absence of visible stages of dissolution of myelin; absence of phagocytes laden with lipoid and of extracellular particles or masses of lipoid material. This was true of the parenchyma, while in the walls of blood vessels large amounts of lipoid were present in adventitial cells. A

few extracellular particles of lipoid material were also demonstrable in the walls. In the angle formed by a branch from a vessel the lipoid material was likely to be more concentrated.

It was impossible to estimate the age of the individual lesions. The criteria available in cases of multiple sclerosis were absent here. The distribution and quantity of lipoid and the glial reaction gave no aid in distinguishing between fresh and older processes. The only criterion for judging the duration of the disease process in various parts of the central nervous system was the number of the focal lesions. Where they were most numerous the process was probably oldest. On this basis, the frontal lobes, or anterior portion of the cerebrum, were affected earlier than the occipital lobes.

The strict perivascular localization of the demyelination raises the question of pathologic changes in the walls of the vessels. The results of examination, however, were without significance. The endothelium was unchanged and the elastic tissue normal. There was no increase of reticulin or collagen fibers, no hyalinization or arteriosclerotic changes and no evidence of recent or organized thromboses or other occlusion. The only abnormal change was some tortuosity of the vessels. This, however, was probably due to the generalized atrophy and was secondary.

There was no demonstrable reaction of the glia to degeneration of the myelin sheaths. Neither in the myelinated areas nor in the marginal zones between them and the normally myelinated tissue was there any proliferation of glia cells—microglia cells, oligodendrocytes or astrocytes.

Focal areas of loss of ganglion cells were present in the cortex. As far as could be determined, these probably did not coincide with the areas of demyelination.

CONCLUSIONS

1. This case is described because of the type of demyelinated lesions and their widespread distribution. The condition was chronic (of approximately thirteen years' duration) and had clinical similarities to multiple sclerosis, although there were many differences. The differences included the preponderance of psychic changes (poor memory for recent events), with poorly developed or only suggestive signs of involvement of the pyramidal tracts; the onset with a peculiar state resembling neurasthenia, of long duration, which had special emotional features (forced laughter accompanied by a suicidal tendency); the absence of a number of symptoms classic for multiple sclerosis (scanning speech, intention tremor and nystagmus) and other symptoms typical of multiple sclerosis, and the occurrence of atypical symptoms, such as complete atrophy of the optic nerves and epileptic seizures. The slow, progressive clinical course without remissions and acute exacerbations was against the diagnosis of multiple sclerosis.

2. Pathologically, the case differed from one of multiple sclerosis. *A*. Grossly, there was atrophy of the cerebrum, cortex and white matter, although there were nowhere any lesions resembling those of multiple sclerosis. The periventricular zones, which are especially susceptible to change in multiple sclerosis, were almost free from lesions.

B. Microscopically, the demyelinated areas were strictly perivascular (or periangiotic). The medium-sized and small veins and arteries were

affected throughout the central nervous system: the cerebral cortex and white matter, basal ganglia, cerebellum, brain stem and spinal cord. The anterior portion of the cerebrum was apparently damaged earlier and more intensely than the posterior portion.

The cerebellum, brain stem and spinal cord had the fewest, and perhaps freshest, lesions. The demyelinated areas were approximately of the same size throughout. Large lesions, similar to those seen in multiple sclerosis, were absent. There were no areas of demyelination about the capillaries. The foci of demyelination were strictly localized about the vessels, so that a vessel was always observed in the central axis of a demyelinated area. The wall of the vessel was not thickened and showed no arteriosclerotic or infiltrative inflammatory changes. There was no evidence of endarteritis, although the endothelial nuclei were somewhat large and definitely indented; they showed no mitoses, however. The adventitial nuclei were strikingly pale, narrow and long, had definite hyperchromatosis of the nuclear wall, but exhibited no mitoses. There were many mast cells, but no adventitial infiltration. Stains for fat revealed little fat as compared with the amount of destruction of myelin, certainly a great deal less than in the corresponding small lesions of multiple sclerosis. The lipoid material was stored in the adventitial layer of the vessels. Compound granule cells were absent or infrequent in the demyelinated parenchyma. The color of the lipoid material in these areas was different from that in the nearby ganglion cells, being yellower in the former and redder in the latter (sudan III). At the bifurcations of the blood vessels the lipoid material was often increased considerably. In contrast to dementia paralytica and multiple sclerosis, the cortical areas of demyelination exhibited the same characteristics as those in the white matter. In multiple sclerosis, as well as in dementia paralytica, a focal lesion affecting both the cortex and the white matter shows a heavy collection of lipoid only in the white matter and a distinct dividing line at the junction of the white and the gray matter between an abundance and a small amount of lipoid. In this case, however, the demyelination and accumulation of lipoid were of the same type in the gray matter as in the white matter. The axis-cylinders in the demyelinated areas were preserved. The glia did not show any definite reaction.

The ganglion cells were pale and contained no Nissl substance (only material fixed in formaldehyde was available, however). Focal areas of loss of ganglion cells seemed to be present without any glial reaction. The glia nuclei in the white matter appeared to be increased in number, but this increase was only apparent, as in the case of every atrophy. There were no formations of large, abnormal-looking glia nuclei, such as are seen in pseudosclerosis and spastic pseudosclerosis (Jakob [13]).

3. The regular character of the demyelination, the homophasic (similar phase) state of the demyelination in nearly all parts of the

13. Jakob, A.: Ueber eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswertem anatomischen Befunde (spastische Pseudosklerose-Encephalomyelopathie mit disseminierten Degenerationsherden), Ztschr. f. d. ges. Neurol. u. Psychiat. **64**:147, 1921.

neuraxis and the constant relation to blood vessels justify a new name: homophasic demyelinating periangiosis.

4. Up to the present no similar pathologic entity has been described. The condition was somewhat reminiscent of that described by Milian and his co-workers [14] as "acute optic neuromyelitis." The softenings and cavity formations described in cases of optic neuromyelitis were absent in my case.

5. The etiologic factors in the disease were obscure. Perhaps the long sojourn at great heights in airplanes played a part, since the disease undoubtedly originated about the blood vessels. Perhaps the accidents also had significance. The chronic, progressive course of the disease, continuing for many years after the patient was no longer exposed to such injuries, is against both these possibilities.

14. Milian; Lhermitte; Schaeffer, H., and Horowitz: La neuropticomyélite aigüe: Observation anatomoclinique, Rev. neurol. **2**:257, 1931.

News and Comment

THIRD INTERNATIONAL NEUROLOGICAL CONGRESS

The Third International Neurological Congress will be held in Copenhagen, Denmark, from Aug. 21 to 25, 1939. In accordance with the usual custom, four days will be devoted to the scientific sessions of the congress. Three symposia will be held on subjects chosen by the Program Executive Committee. A morning and an afternoon session will be devoted to the consideration of each of these topics, one day being devoted to each subject. The following subjects will constitute the symposia:

1. The Autonomic Nervous System, with Special Reference to the Endocrine System.

2. Heredofamilial Disease, Especially from the Genetic Aspect.

3. Neurologic Aspects of the Avitaminoses, with Especial Reference to the Peripheral Nervous System.

The programs for these special subjects have been planned by special chairmen, and invitations have been issued to those particularly interested in these fields to prepare papers for presentation before the congress. Professor van Bogaert and Professor Pette have arranged the program for the symposium on the autonomic nervous system; Professor Guillain, for that on heredofamilial disease, and Professor Monrad-Krohn, for that on neurologic aspects of the avitaminoses. Five reporters will contribute papers to the dicussion of each of the three chosen topics, each communication being limited to twenty-five minutes.

The sessions of the congress will be held in the Houses of Parliament in Copenhagen.

One day of the congress will be devoted to the presentation of short papers by active members of the congress. No member will be allowed to present more than one communication. The presentation of these miscellaneous communications will be limited to ten minutes. As far as possible, these shorter papers will be grouped under appropriate topics, and special sessions of the congress will be arranged for the presentation of the papers. Active members desiring to present short papers before the congress must furnish to the secretary of the Committee for the United States a title and an abstract not exceeding 200 words on or before March 1, 1939. The titles and accompanying abstracts will then be considered by the committee representing the United States, and as soon as possible the contributor will be notified whether his paper has been tentatively accepted. The titles accepted by the committee representing the United States will then be forwarded, together with the abstracts, to the Danish Program Committee for final action. Proposers of papers will probably be notified on or about May 1, 1939, whether the paper has been accepted by the Danish Program Committee.

In accordance with the usual custom, Wednesday of the week of the congress will be devoted to excursions in the vicinity of Copenhagen.

Membership in the congress will be comprised of active and associate members. Applicants for active membership must belong to some national or local neurologic, psychiatric or neuropsychiatric association or society and must secure endorsement of their application by the local association or by a neurologist or psychiatrist known to the Committee for the United States. The fee for active membership is $8.

Members of families, physicians in other specialties and nonmedical persons engaged in fields of activity associated with neurology and psychiatry may apply for associate membership. The fee for associate membership is $4. Application blanks for active and associate membership may be obtained by application to the secretary of the Committee for the United States.

The American Express Company has been appointed as the official travel agency for the Third International Neurological Congress. In order to obtain the most satisfactory results, arrangements for travel or for hotel accommodation should be made through the American Express Company. Arrangements for travel may, of course, be made through any travel agency, but in order to secure suitable hotel accommodations in Copenhagen arrangements for rooms should be made through the American Express Company. In view of the considerable number of persons expected to attend the congress and the relatively limited accommodations existing in Copenhagen, early application for room reservations should be made.

Canadian neurologists and psychiatrists interested in attending the congress should communicate with Dr. Wilder Penfield, vice president representing Canada.

The officers of the Third International Neurological Congress are: Honorary Presidents, Dr. Gordon Holmes, Dr. B. Sachs and Sir Charles Sherrington.

Honorary Member from the United States, Prof. Harvey Cushing; president, Prof. Viggo Christiansen; general secretary, Dr. Knud H. Krabbe; local secretary, Dr. C. J. Munch-Petersen; treasurer, Dr. Einar Sorensen; editor of transactions, Dr. Knud Winther.

The vice presidents of the congress have been chosen from 22 constituent countries, 1 from each locality.

Transactions consisting of abstracts of presentations and discussions, together with other pertinent details concerned with the conduct of the Third congress, will be published in due course of time after the conclusion of the congress.

As no title or abstract will be accepted by the Danish Program Committee unless at that time the author is an active member of the congress, application blanks for membership properly filled out, together with check in payment of the membership fee, should accompany the submission of the title and abstract, and should be addressed to Dr. Henry Alsop Riley, secretary, 117 East Seventy-Second Street, New York.

Dr. B. Sachs, Chairman
Dr. Henry Alsop Riley, Secretary
Dr. Foster Kennedy
Dr. John Fulton
Dr. S. W. Ranson
Dr. Stanley Cobb

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION

The sixteenth annual meeting of the American Orthopsychiatric Association, an organization for the study and treatment of behavior and its disorders, will be held at the Commodore Hotel, Lexington Avenue and Forty-Second Street, New York, on Feb. 23, 24 and 25, 1939. Secretary: Dr. Norvelle C. La Mar, 149 East Seventy-Third Street, New York.

Abstracts from Current Literature

Anatomy and Embryology

Diurnal Changes in the Retina of the Catfish, Ameiurus Nebulosus. John H. Welsh and Clinton M. Osborn, J. Comp. Neurol. **66**:349 (April) 1937.

This study was carried out to determine whether the rods, cones and pigment in the eyes of the catfish underwent changes from day to night in the absence of normal periods of light and dark. Catfishes were exposed to constant illumination or to constant darkness and killed either during the day or at night. Welsh and Osborn observed significant measurable differences in the lengths of the myoid segments of both rods and cones in the eyes of animals kept in the dark for twenty-four hours depending on whether they were killed in the daytime or at night. The average length of rod myoids in a retina adapted to dark and removed at night was 7.64 microns; that for rod myoids of a retina similarly adapted but removed during the day was 14.33 microns. The cone myoids in these retinas were twice as long in the animals killed at night as in those killed in the daytime. This persisting "diurnal rhythm" continued for at least two days, in the absence of recurring external stimuli. The results on movement of pigment were inconclusive.

Addison, Philadelphia.

Total Distribution of Taste Buds on the Tongue of the Kitten at Birth. Rush Elliott, J. Comp. Neurol. **66**:361 (April) 1937.

Elliott studied the tongues of 4 newborn kittens to determine the distribution of taste buds. The average size of the taste buds was 20 microns, and the average number, 473. No buds were noted on the ventral or lateral surfaces of any portion of the tongue. None was seen on the extreme tip or the extreme base of the tongue; 229 buds were counted on the middle third, and over 222, on the posterior third. These were observed, mostly on the tips of the fungiform papillae, there being usually 4 or less to a papilla. Many of the fungiform papillae possessed no taste buds.

Fraser, Philadelphia.

Structural Variations of the Visual Cortex in Primates. Gu Ngowyang, J. Comp. Neurol. **67**:89 (June) 1937.

Ngowyang studied the cerebral hemispheres of Macacus cynomolgus and the baboon, orang-utan and chimpanzee after staining for tigroid substance or myelin. Many new structural variations of the visual cortex were revealed. The area striata in monkeys had the largest surface extension, especially on the lateral convexity of the hemisphere, where it extended as far rostral as the margin of the sulcus simialis. The brain of the gibbon suggested an anthropoid type of configuration. Variations in the arrangement of cell layers in the visual cortex were observed, and an explanation is offered for the origin of the sublayers of the fourth layer of the area striata. Ngowyang observed that the asymmetric distribution of the area striata in relation to the fissura calcarina is common to all primates. He concludes that there is no absolute clearcut demarcation between the higher and the lower forms of primates with regard to fissural pattern and areal configuration and distribution.

Fraser, Philadelphia.

MORPHOLOGICAL COLOR CHANGES IN FISHES. J. M. ODIORNE, J. Exper. Zoöl. **76**:441 (Aug.) 1937.

The influence of white and black backgrounds on the number of melanophores or the amount of pigment contained in them was studied in Fundulus majalis Walb., Ameiurus nebulosus Lesueur (catfish), very young paradise fish (Macropodus opercularis) and older, but immature mosquito fish (Gambusia sp.). In fishes kept on white backgrounds pigmentation was reduced through degeneration of melanophores or retardation in the development of melanophores in the young specimens. In fishes kept on black backgrounds the melanophores increased. Blinded catfishes kept in the light became extremely dark, but suffered a slight reduction in pigmentation if kept in darkness. The light reflected to the eyes by the surroundings is evidently a factor of great significance. When development of pigmentation is retarded or degeneration of melanophores occurs the pigment is in the aggregated state. Conversely, when increase in pigmentation occurs the pigment within the chromatophores is dispersed. It is suggested that conditions which bring about aggregation of pigment in the melanophore will, if maintained, inhibit the further development of melanophores, or even cause the destruction of some of those already present. Conditions leading to dispersion of pigment throughout the cell will, if maintained, promote the development of melanophores. According to this view, morphologic and physiologic color changes are phenomena resulting from a common cause, the former not depending on the latter, as has previously been suggested. It is also suggested that the neurohumors which cause the pigmentary migrations in Fundulus exert trophic influences on the melanophores.

WYMAN, Boston.

BLOOD VESSELS IN TRANSPARENT PREPARATIONS OF THE BRAIN: I. VESSELS OF THE CORNU AMMONIS. MARCEL HEIMAN, Schweiz. Arch. f. Neurol. u. Psychiat. **40**:277, 1938.

Heiman studied the cerebral vessels by means of preparations of the brain rendered transparent by the method of Spalteholz. The hippocampus was selected for study. The uncus usually receives its blood supply from an anastomosis formed by branches of the anterior choroidal artery and the proximal hippocampal branch of the posterior cerebral artery, but it may receive its entire supply from the posterior cerebral artery. The two to five branches of the posterior cerebral artery which enter the cornu ammonis are termed the primary hippocampal vessels. Bifurcating branches of these vessels anastomose with each other to form an arcade or series of vascular loops along the horizontal axis of the hippocampus. The proximal branch of the first vessel in this series usually unites with a branch given off by the anterior choroidal artery before the latter enters the choroid plexus. Vessels arising from the vascular loops are termed the secondary hippocampal vessels. In addition to these arteries, branches of the primary hippocampal vessels at times enter the cornu ammonis directly, but in spite of this and other anomalies the arcade arrangement is constant and unique for this part of the brain. The secondary hippocampal vessels proceed to the dorsal, lateral and ventral portions of the cornu ammonis, where they divide into a number of terminal branches, which are not demonstrated equally well in all preparations. In addition to the secondary hippocampal vessels, others extend from the vascular loops to the region of the end leaf. Since there appear to be no anastomoses between the secondary hippocampal vessels and since capillary anastomosis does not protect cerebral tissue from the hazard of vascular occlusion, these vessels are to be regarded as anatomic end arteries. There is, furthermore, no overlapping of the terminal branches.

Although the area of distribution of the lateral secondary hippocampal vessel corresponds roughly to Sommer's sector, there is so much individual variation in the territory supplied by the different vessels that morphologic units cannot be said to have a constant source of blood supply. As the vessel in question differs from the others only in its somewhat longer course, Spielmeyer's assumption of a vascular basis for the peculiar vulnerability of Sommer's sector in cases of sclerosis

of the cornu ammonis is hardly justified anatomically. The degenerative changes not necessarily being limited by morphologic boundaries, Vogt's theory of pathoclisis also does not account entirely for their distribution. DANIELS, Denver.

Physiology and Biochemistry

OXYGEN WANT AND INTRACRANIAL PRESSURE. J. MICHELSEN and J. W. THOMPSON, Am. J. M. Sc. **195**:673 (May) 1938.

Michelsen and Thompson report on the symptoms produced by the experimental induction of anoxemia by reduction of oxygen tension in a chamber. Almost all the subjects who were exposed to low oxygen pressure after approximately two hours complained of headache, followed by repeated, or even continuous, yawning and sighing. In 2 subjects projectile vomiting and a slow pulse rate were noted after the intense headache. In 1 subject the mental state was characterized by stupor, in which volition was at a minimum. The reduction of the oxygen saturation of arterial blood seems to have no quantitative relation to the severity of the clinical manifestations. MICHAELS, Boston.

THE WORK PERFORMANCE OF UNTREATED HYPOPHYSECTOMIZED RATS. D. I. INGLE, Endocrinology **22**:465 (April) 1938.

Ingle studied the work capacity of the gastrocnemius muscle of the hypophysectomized rat by means of faradic stimulation. At varying periods subsequent to operation the capacity for work was determined for (*a*) totally hypophysectomized animals, (*b*) animals in which the anterior lobe of the hypophysis had been removed and the posterior lobe left intact and (*c*) animals in which half of the anterior lobe of the hypophysis had been removed and the posterior lobe left intact. It was found that when the muscle was stimulated immediately after total hypophysectomy the rate of work was normal during the first few hours but rapidly decreased to a point at which muscular responsiveness was completely lost. There was an inverse relationship between the capacity of the muscle to perform sustained work and the interval between operation and the beginning of the work test. The presence of the posterior lobe of the pituitary gland did not protect the animal against the deficiencies in work capacity which developed when the anterior lobe was completely removed. When half of the anterior lobe was left intact, the work performance of the rat was carried out at nearly normal levels. PALMER, Philadelphia.

CHEMICAL STUDIES ON THE NEUROPROTEINS: II. THE EFFECT OF AGE ON THE AMINO ACID COMPOSITION OF HUMAN AND MAMMALIAN BRAIN PROTEINS. RICHARD J. BLOCK, J. Biol. Chem. **120**:467, 1937.

Proteins prepared from the brains of 5 normal human males, varying in age from 4 to 82 years, were analyzed for nitrogen, histidine, lysine, arginine, tyrosine and tryptophan. The molecular ratio of lysine and arginine in the human neuroproteins remained remarkably constant throughout the entire age group. Neuroproteins of primates, rodents and ungulates yield on hydrolysis approximately the same amounts of histidine, arginine, lysine, tyrosine and tryptophan. The data suggest that neuroproteins prepared from young mammals yield less histidine than those obtained from adults. PAGE, Indianapolis.

ACTIVATION OF HEAT LOSS MECHANISMS BY LOCAL HEATING OF THE BRAIN. H. W. MAGOUN, F. HARRISON, J. R. BROBECK and S. W. RANSON, J. Neurophysiol. **1**:101 (March) 1938.

Local heating of the brain of the cat with a low voltage, high frequency current passing between electrodes oriented with the Horsley-Clarke apparatus demon-

strated a reactive region which responds to heating by marked acceleration of respiratory rate, panting and, in some instances, appearance of sweat on the foot pads. The reactive elements appear to be concentrated in the mediocaudal part of the ventral portion of the telencephalon and, in lesser concentration, are continued backward through the diencephalon as far as the anterior end of the midbrain. In the telencephalon, the responsive region occupies a position between the anterior commissure and the base of the brain. In the diencephalon, it is located in the dorsal part of the hypothalamus and the ventral part of the thalamus and occupies a progressively more dorsal position caudally. At the anterior end of the midbrain it is located in the vicinity of the central gray matter surrounding the transition from the third ventricle to the cerebral aqueduct.

The results are interpreted as indicating that the reactive region contains structures which are activated by the rising temperature of the blood and in the normal animal when overheated lead to activity producing loss of heat.

ALPERS, Philadelphia.

ELECTRICAL EXCITABILITY OF THE MOTOR FACE AREA. A. EARL WALKER and HAROLD D. GREEN, J. Neurophysiol. **1**:152 (March) 1938.

Walker and Green studied the responses of the motor area for the face in monkeys, baboons, chimpanzees, 1 mangabey and 1 spider monkey. Stimulation of area 4 elicited a brief contraction of an individual muscle of the contralateral side of the face or a smooth, sustained contraction of a group of muscles. Stimulation of the tongue area caused deviation and rotation to either side. These responses were present from area 4 even after area 6 had been removed. Hence the response from area 4 is regarded as independent of any adjacent cortical area.

The threshold of area 6 was found to be higher than that of area 4. Stimulation of area 6 a α gave rise to complex movements of groups of facial muscles, but never to twitches of individual muscles. Entire ablation of area 4 largely destroyed the responsiveness of area 6 a α. Excitation of area 6 b β produced rhythmic opening and closing of the mouth, with or without protrusion and retraction of the tongue. Excitation of area 6 b β produced alteration of respiration characterized by temporary cessation or diminution of excursion. The response was found to be independent of the motor area or other portions of the premotor cortex. In two experiments excitation of the cortex caused bilateral, or occasionally contralateral, movements of the orbicularis oculi or frontalis muscle. In 1 case Walker and Green observed ipsilateral contraction of the musculature of the lower part of the face as the result of cortical excitation.

ALPERS, Philadelphia.

THE RELATIVE VASCULARITY OF DIFFERENT AREAS OF THE MAMMALIAN BRAIN. A. COLIN P. CAMPBELL, J. Ment. Sc. **83**:510 (Sept.) 1937.

Campbell made comparative studies of the vascularity of the basal ganglia and the cerebral and cerebellar cortex of the cat. The capillaries were demonstrated by injection of india ink and the results expressed in millimeters of capillaries per cubic millimeter of tissue. The results indicate a striking difference in vascularity in the various areas of gray matter examined; the globus pallidus was observed to be by far the least vascular area; the basal ganglia were on the whole less vascular than the cerebral or the cerebellar cortex. The lateral geniculate body had a high vascularity.

To a certain extent, Craigie's statement that the receptive and associative areas have a higher vascularity than the efferent areas was confirmed. Furthermore, a correlation could be made between the vascularity and the population of ganglion cells of the various areas. There were striking exceptions to this correlation, such as the granular layer of the cerebellum, which has a relatively low vascularity in view of its extremely dense cellularity. This, like the demonstration of the relatively low vascularity of the cat's trigeminal ganglion by

Dunning and Wolf, suggests that the metabolic activity of an area of nerve tissue is not necessarily in proportion to its richness in ganglion cells. The relationship, if any, of richness or poverty of capillary development to the selective localization of anoxemic lesions remains obscure. That selective necrosis in carbon monoxide poisoning occurs in the globus pallidus, the least vascular area of gray matter so far examined, is superficially suggestive; while the vascularity of this area is poor, however, its oxygen need for survival also may be low, and there is no means as yet of knowing whether in this, or any other area, a low margin exists between anatomically available capillary bed and oxygen need.

AUTHOR'S ABSTRACT.

EVIDENCE FOR ELECTRICAL TRANSMISSION IN NERVE. A. L. HODGKIN, J. Physiol. **90**:167, 1937.

A nerve impulse produces a large increase in excitability and an "extrinsic potential" due to electrotonic spread beyond a region of block. Evidence is offered to show that the electrotonic current is the cause of the increase in excitability. The average change in excitability is from one and four-tenths to two and three-tenths times as large as that produced by an applied electrotonic potential of the same form. The author concludes that it is possible for nerve impulses to be transmitted by electrotonic currents.

McCOUCH, Philadelphia.

ASCENDING SPINAL PATHWAYS OF THE PUPILLO-DILATOR FIBRES. A. A. HARPER and B. A. McSWINEY, J. Physiol. **90**:395, 1937.

In acute experiments on cats under anesthesia induced with a compound of chloral hydrate and dextrose (chloralose), pupillary dilatation from stimulation of the central ends of the cut splanchnic and intercostal nerves was studied before and after a variety of partial sections of the spinal cord in the cervical region. Bilateral section of the lateral columns abolished the effect; unilateral section did not. The ascending fibers cross one segment above the root of entrance of the afferent fibers concerned.

McCOUCH, Philadelphia.

PRODUCTION OF EXPERIMENTAL CATATONIA BY THE USE OF METRAZOL. A. LEROY and P. CLEMENS, J. belge de neurol. et de psychiat. **37**:485 (Aug.) 1937.

Leroy and Clemens produced epileptiform convulsions in mice by the use of metrazol. Preceding the convulsions they noted a brief period during which the animals demonstrated many of the characteristics of catatonia, namely, inertia, indifference, negativism and transient catalepsy. They were able to regulate the dose so that the convulsive and cataleptic phenomena were dissociated. The reactions in the various animals were neither constant nor specific, and individual tolerance seemed to be of some importance. The symptoms resembled "insulin catalepsy," the experimental catatonia following the use of bulbocapnine, and clinical catatonia.

DE JONG, Ann Arbor, Mich.

PARADOXIC DILATATION OF THE PUPIL. A. LÁNCZOS, Arch. f. d. ges. Physiol. **238**:546, 1937.

Extirpation of both upper cervical ganglia in frogs on the same day produces miosis of both pupils. A two stage operation produces different effects, the extirpation of the second ganglion inducing transient dilatation of the pupil on the side of the first extirpation. This dilatation lasts from one to two hours only; it is more pronounced and lasts several days if the vagus and glossopharyngeus nerves are also cut. Unilateral section of the vagus and glossopharyngeus nerves alone may produce marked dilatation of both pupils. Severance of the oculomotor nerves prevents this phenomenon. This is a reflex effect, due to stimulation of afferent

fibers of the ninth and tenth nerves which are pulled during extirpation of the upper cervical ganglion. These afferent stimuli reflexly inhibit the oculomotor nuclei. This transient reflex phenomenon is apparently different from the slowly developing and permanent pupillary dilatation developing after extirpation of the upper cervical ganglion (Langendorff phenomenon) and should not be considered an analogue to the latter phenomenon.

SPIEGEL, Philadelphia.

BILIRUBIN CONTENT OF THE BLOOD SERUM IN PSYCHOSES. J. A. T. LIGTERINK and C. A. SIMONS, Psychiat. en neurol. bl. **41**:369, 1937.

The serum bilirubin content during fasting was determined in 21 schizophrenic, 12 depressed and 11 manic patients, 4 patients with involutional melancholia, 4 with dementia paralytica and 7 with other types of psychoses. The serum bilirubin was found to be increased in a number of patients during the active stages of schizophrenia and manic-depressive psychosis. During this period they were restless, ate poorly and lost weight. The authors, confirming Lingjaerde's experience, assume that the hepatic insufficiency underlying the increase of bilirubin is due to a relative or absolute insufficiency in carbohydrate intake. Another explanation may be the higher concentration in the blood, the presence of which was inferred from the increased total protein content of the blood.

LEWY, Philadelphia.

THE p_H OF THE BLOOD IN EXPERIMENTAL CONVULSIONS INDUCED WITH METRAZOL. HELMUT SELBACH, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:334 (Nov.) 1937.

Selbach studied the p_H of the blood after the injection of metrazol in 23 guinea pigs. Metrazol produces first a hyperpneic phase, accompanied by a vasoconstriction in the ear and eyegrounds, and later a tonic phase, with apnea and hyperemia. The tonic phase lasts from twenty to twenty-five seconds. The duration of the clonic phase varies more, but rarely exceeds fifty seconds. During the initial hyperpneic stage alkalosis of the blood was noted. This changed to acidosis toward the end, but also during the first half, of the tonic phase. Hyperemia in the ear and fundi was noted in association with the acidosis. With subliminal doses of metrazol, intravenous injections of an alkali did not induce convulsive attacks. This shows that the alkalosis alone cannot be responsible for the convulsive attack. Vasoconstriction of vessels supplying important parts of the brain calls forth a generalized intensification of motor activity with acidosis. This acidosis has been shown to favor widening of the vascular bed and to overcome the tendency to vascular constriction. The convulsions with the accompanying acidosis are therefore a protective mechanism to insure the proper blood supply to the vital centers in the medulla.

SAVITSKY, New York.

Neuropathology

PALATOPHARYNGOLARYNGEAL MYOCLONUS ASSOCIATED WITH A LATEROBULBAR NEURINOMA. E. DE SAVITSCH and R. A. LEY, Rev. neurol. **67**:585 (May) 1937.

In most of the cases of palatal myoclonus reported the cause was a vascular lesion. In only 2 cases was there a tumor, that reported by Spencer (*Lancet* **2**:702, 1886) and that by S. A. K. Wilson (*Brain* **43**:229, 1920). The case reported here was that of a woman aged 37 who had a large meningoblastoma in the right cerebellopontile angle, arising from the internal auditory meatus. This was removed for the most part at operation. After transient improvement, renewal of the symptoms led to a second operation. A subarachnoid cyst was evacuated; remains of the tumor were removed, and the region was irradiated.

Bitonal phonation, clonic respiration and typical bilateral nystagmus of the palate, pharynx and vocal cords appeared. The contractions were more ample in the left than in the right vocal cord. Death occurred two years after the first operation. Necropsy revealed a firm tumor, the size of "a small apple," depressing deeply the medulla and the ventral aspect of the right cerebellar hemisphere. The left superior cerebellar peduncle was entirely atrophied. The restiform body, nucleus cuneatus and descending trigeminal root on the right side were greatly compressed. The dentate nuclei of the cerebellum were both degenerated, the right more than the left. The left bulbar olive showed intense demyelination and pseudohypertrophy; both the intraciliary and the extraciliary fibers were involved, the latter chiefly in the ventrolateral lamellae. The right olive showed slight degenerative lesions, but no hypertrophy. The left red nucleus contained rarified ganglion cells. The central tegmental bundles were intact.

LIBER, New York.

TRAUMATIC LESION OF THE OPTIC NERVE WITHOUT ASSOCIATED FRACTURE OF THE SKULL. G. B. BELLONI, Riv. oto-neuro-oftal. **14**:521, 1937.

Belloni reports a case in which the patient suddenly noticed, after an automobile accident, in which he sustained an injury to the head but was not unconscious, that vision of the right eye was lost. There were at first no other neurologic manifestations, but meningitis developed and the patient died a week after the accident. Autopsy demonstrated that there was no fracture of the optic canal or clinoid processes but that there were contusion and hemorrhagic infiltration of the lower portion of the optic nerve.

PUTNAM, Boston.

SENILE ATROPHY OF THE CEREBELLUM: PERSISTENCE OF PERICELLULAR BASKETS AFTER DISAPPEARANCE OF THE PURKINJE CELLS. B. A. MOYANO, Arch. argent. de neurol. **17**:23, 1937.

In a case of senile dementia, terminating in death at the age of 78, necropsy showed diffuse atrophy of the cerebrum with enlargement of the ventricles and atrophy of the cerebellum, confined mainly to the superior portion of the vermis. Histologically, this area showed complete disappearance of Purkinje cells and climbing fibers, with great thickening of the fibers composing the pericellular baskets, which had filled in the space left by the Purkinje cells. The horizontal fibers appeared to be intact. The molecular and granular layers were thinned, and there was some loss of myelin in the granular layer and in the white matter. Neuroglial proliferation was present in the damaged areas.

This lesion was degenerative with highly selective characteristics, in that the effector mechanism only was destroyed. In it were demonstrated to a degree the character of the synaptic connection between the basket fibers and the Purkinje cells and the anatomic and trophic independence of each neuron.

NORCROSS, Philadelphia.

CORTICAL ATROPHY IN THE ADULT. V. DIMITRI and J. ARANOVICH, Rev. neurol. de Buenos Aires **1**:452, 1937.

The authors report the case of a man aged 42 admitted to the hospital in coma. The Wassermann reaction was negative. Autopsy showed a carcinoma of the stomach, with arteriosclerosis and nephrosclerosis. In the brain there was fairly widespread ischemic necrosis, with perivascular reaction and glial proliferation. Grossly, many fine pitted depressions were visible on the surface. The damaged areas microscopically showed numerous small foci surrounding small blood vessels. The neurons in such zones had disappeared, and those of the periphery showed various stages of degeneration.

KING, Princeton, N. J.

BRAIN OF THE "OLDEST MAN IN THE WORLD" (ZARO AGA). I. SCHÜKRÜ-AKSEL, Arch. f. Psychiat. **106**:260 (Jan.) 1937.

Schükrü-Aksel reports a neuropathologic study of the brain of Zaro Aga, who died in 1934, at the given age of 156 and the probable age of at least 130. The immediate cause of death was pulmonary tuberculosis and uremia. The brain showed a pronounced deposit of lipoids in the ganglion and glia cells. In addition, there were diffusely scattered, peculiar-looking, large pale glia nuclei with little cytoplasm. These cells showed certain similarities to those observed in pseudosclerosis, but their nature and origin are unknown. There was little atrophy, and only a few senile plaques were observed in one area of the frontal lobe.

W. MALAMUD, Iowa City.

CLINICAL AND HISTOPATHOLOGIC STUDY OF HEREDITARY SPASTIC PARALYSIS. A. KAHLSTORF, Ztschr. f. d. ges. Neurol. u. Psychiat. **159**:774 (Sept.) 1937.

Kahlstorf reports the anatomic changes in a case previously reported by Specht (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **99**:477, 1922). The onset of the illness was at the age of 31. Death occurred at 63. The disease began insidiously. The progress was slow and relentless. There were no remissions. The positive neurologic findings were spastic paraplegia and a Babinski sign on the left. The right plantar response could not be evaluated because of deformity of the right foot secondary to trauma. Sensory changes were not reported. The pupils reacted normally. There was a family history of a similar illness in 11 of 17 members, of three generations. Sex linkage did not appear. Histologic examination of the nervous system revealed degeneration of the pyramidal system, especially of the lateral tracts, demyelination in Goll's columns and the spinocerebellar tracts, hypoplasia of the cerebellum, marked atrophy of the basal ganglia and diminution of the number of Betz cells in the prefrontal cortex. Kahlstorf comments on the possibility of spastic paraparesis due to intracortical cellular degeneration. Schaffer and Spielmeyer have called attention to such intracortical spastic paralyses. Involvement of Goll's columns was present without sensory changes. Kahlstorf could not confirm the observation of Strümpell that coexistent degeneration of Goll's columns reduces spasticity. In the author's case spasticity was so severe that the left obturator nerve had to be cut to relieve the adductor spasm. The presence of cerebellar hypoplasia and the involvement of the cerebellar tracts indicate that the degenerative process is not always limited to the pyramidal tracts and that the problem is more complex than can be explained by isolated degeneration of the lateral columns.

SAVITSKY, New York.

CLINICAL AND ANATOMIC STUDIES IN A CASE OF CHOREA MINOR. G. G. NOTO, Ztschr. f. d. ges. Neurol. u. Psychiat. **159**:781 (Sept.) 1937.

Noto reports the case of a woman aged 60 who on Dec. 3, 1933, felt feverish and the next day complained of pains in the joints. She was treated with salicylates for a few weeks. After a few days dyspnea, tachycardia and mitral insufficiency were found. At the same time she had bilirubinuria and hyperbilirubinemia. After this attack, toward the end of February 1934, she began to show choreic movements on the left side. The clinical picture was definitely that of chorea. The movements continued to be most marked on the left side. They were less marked in the lower limbs, ceased during sleep and were worse during emotional upsets. The tongue was involved in the movements. The muscular power was weakened throughout. There was bilateral dysdiadokokinesis. The deep reflexes were depressed. The pupils reacted sluggishly to light and somewhat better in accommodation. Serologic tests of the spinal fluid gave negative results. The mastic curve was normal. The patient died on May 2, in status choreicus. Autopsy showed recent endocarditis, with infiltration of the cardiac muscle and Aschoff bodies. There was hyperemia of the meningeal and cerebral vessels, but no perivascular

infiltration. There were diffuse changes in the ganglion cells, involving especially the cells of the cerebral cortex and the cerebellum. Tigrolysis, pyknosis and pigmentary and vacuolar degeneration were observed. No significant changes were seen in the walls of the blood vessels. Noto notes the advanced age of this patient with rheumatic fever and chorea minor. Anatomically, the absence of evidence of inflammation was noteworthy. Noto adds that this may be correlated with the relatively long duration of the illness. The diffuse changes in the ganglion cells were the only pathologic observations. The basal ganglia were not especially involved.

SAVITSKY, New York.

HISTOPATHOLOGIC CHANGES IN THE CENTRAL NERVOUS SYSTEM ASSOCIATED WITH SCHIZOPHRENIA. T. HIRESAKI, Psychiat. et neurol. jap. **41**:95 (Dec.) 1937.

Hiresaki investigated 30 cases of schizophrenia. In 2 cases of acute catatonic excitement he found universal acute cell disease (Nissl), axonal chromatolysis of the Betz cells, in 1 case, progressive changes in the astrocytes and oligodendroglia cells, glial proliferation and, at times, progressive changes in the microglia cells. In 3 cases of chronic catatonic excitement he observed slight architectural changes in the frontal pole and in the parietal and temporal areas; in addition there were acute cell disease in all cortical cells, cell sclerosis in the second and third cortical layers, axonal chromatolysis involving the Betz and large pyramidal cells, in 2 cases, destruction of the neurofibrils within the cells and progressive glial changes.

The cortical architecture was disturbed in 10 of 15 cases of catatonic stupor. The areas involved were the frontal, parietal and temporal regions. The third layer was involved chiefly, and the fifth, to a lesser degree. Cell sclerosis and severe cell disease were seen in 11 cases, chiefly in the second and third cortical layers; acute cell disease was present in 4 cases, axonal chromatolysis in 14 cases, loss of nerve fibers in 9 cases and progressive glial changes in many cases. In 2 cases of the hebephrenic form of schizophrenia, slight disturbance in cortical architecture was observed. Cell changes similar to those in cases of the catatonic stupors were observed. Similar alterations were present in 3 cases of paranoid schizophrenia. The chief location of the changes was in the cortical association centers. The axonal chromatolysis and acute cell disease were regarded as evidence of autointoxication. Cell sclerosis was seen in cases of more chronic excitement.

ALPERS, Philadelphia.

LOCALIZATION OF THE HISTOLOGIC LESIONS IN CASES OF THE KORSAKOFF SYNDROME. S. KRNYEY and H. SAETHRE, Acta psychiat. et neurol. **12**:491, 1937.

Several writers have pointed out the similarity of the histologic lesions in Wernicke's polioencephalitis haemorrhagica superior and Korsakoff's psychosis. The differences in the clinical picture of these two conditions are probably due to the differences in the topographic relations of the lesions in the brain. The authors report 3 cases of Korsakoff's psychosis. Histologic examination of the brains showed that, except for more or less marked fatty infiltration, the cortex in all 3 cases was practically free from lesions. In all 3 cases the mamillary bodies showed heavy deposits of fat, intense proliferation of the tissue of the walls of the blood vessels and increase in capillaries. The ganglion cells were relatively spared. The lesions in the wall of the third ventricle dorsal and dorsorostral to the mamillary bodies were absent in the first case, but were severe and extensive, involving the lateral wall of the ventricle from the anterior nucleus of the thalamus to the pulvinar, in the second and third cases. The tuber cinereum was intact in all 3 cases. The lesions caudal to the mamillary body, in the region of the aqueduct, were mild in the first case, more severe in the second and extremely severe in the third. The region of the oculomotor nucleus was especially involved. Thus, in 3 cases of Korsakoff's psychosis in which different clinical pictures were presented the topographic relations of the cerebral lesions were likewise different. The authors

conclude that the symptoms of Korsakoff's psychosis and of Wernicke's disease are due to involvement of the mamillary bodies and the wall of the third ventricle and that the caudal extension of the lesion involving the caudal portion of the thalamus and the aqueduct is associated with severe disturbances of consciousness.

YAKOVLEV, Waltham, Mass.

Psychiatry and Psychopathology

A STUDY OF INSTABILITY, USING THE GOODENOUGH DRAWING SCALE. M. BRILL, J. Abnorm. & Social Psychol. **32**:288 (Oct.-Dec.) 1937.

A person may be equipped with little intelligence and yet may make a normal social adjustment. On the other hand, there are persons who have about the same amount of mentality and yet are social misfits because of emotional instability. This fact is easily proved in an institution for the mentally deficient, where one finds persons who will be able to return to the community and adjust satisfactorily under supervision after a period of serious social and vocational education. In the same community of mentally defective patients are those who, although of the same mental level as the first group, do not profit by social and vocational training and will therefore never be able to adjust in the ordinary community.

The purpose of Brill's study was to determine how well the intelligence scale based on the Goodenough drawing test differentiates between socially adjusted and socially maladjusted mentally deficient persons. The two groups were equated with respect to nationality and race, sex, chronologic age, Binet test age, number of years in the colony prior to the study and general physical health. The abbreviated Goodenough Draw-a-Man test was given, and the drawings of the two groups were scored. The results were compared with the evidence of continuous social adjustment as rated on the Vineland adjustment score card. The conclusions reached were: 1. There is a strong probability (99 chances in 100) that the adjusted group will always score higher on the Goodenough scale than the maladjusted group. 2. This difference is not sufficiently conclusive to be of diagnostic value in individual cases. 3. There is a strong probability (99 chances in 100) that the adjusted group will have a higher Goodenough test age than is expected from the Binet scale; there are only 63 chances in 100 that the maladjusted group will have the same. 4. Thus, a mentally deficient boy who scores approximately two years or more higher on the Goodenough than on the Binet scale belongs probably in the adjusted group; on the other hand, a mentally deficient boy who scores approximately two or more years lower on the Goodenough than on the Binet scale belongs probably in the maladjusted group..

WISE, Howard, R. I.

THE EMOTIONAL REACTIONS OF PSYCHOTIC INDIVIDUALS. JOSEPH C. SOLOMON, J. Abnorm. & Social Psychol. **32**:395 (Oct.-Dec.) 1937.

Solomon has devised a test situation which furnishes a ready means of ascertaining the emotional contact with reality, quantitatively expressed. The test is performed by placing two glasses of water or colored solution on the backs of the outstretched hands of a subject until a response of annoyance is elicited. The glasses are then taken off the hands of the subject and placed on a table with other glasses presumably filled with the same liquid; among these is at least one trick glass which looks exactly like the glasses containing the solution but does not spill. The trick glass is picked up, and after the attention of the subject is adequately secured, a quick move is made as if to pour its contents in his face. The normal response is a defensive reaction based on fear. This is followed by amusement and, finally, curiosity.

The test offers a new set of stimuli to which the subject reacts. The reactions that are elicited are not based to any extent on previous experience. For that

reason, it can be said that the responses are more closely bound to primitive forces than to other previously experienced stimuli which already have affective coloring from associated events. The responses may, therefore, in a measure be considered infantile, for they are not subject to the "memory islands" of unconscious feeling association that may be elicited with other types of emotional testing.

Each of the four observed emotional responses, viz., annoyance, defense, amusement and curiosity, are rated on a scale of 1 to 5; e. g., a marked defense reaction as indicated by bringing the hands to the face is rated as 5. If there is only a noticeable blinking of the eyes the score is recorded as 1. Not only does the objective response serve to place the rating but, in addition, the patient's subjective impression as subsequently narrated is taken into account. The test was made on 125 psychotic patients at the Kings Park State Hospital, of New York. There was marked diminution in emotional responses to these tests among all types of psychotic patients. When the patients were subdivided into diagnostic groups, the following observations were made: There was a striking lack of emotional display in schizophrenic patients. The self-protecting instincts were the last to suffer in regressive states. The responses of the manic patients were decidedly similar to those of the patients of the hebephrenic group and entirely unlike those of normal persons. The emotions which manic patients display in their psychotic behavior seem to be related only to their own ideational content and not to any external stimuli. The depressed patients, on the other hand, demonstrated much higher degrees of emotionality than either the manic or the schizophrenic patients. The reactions in the involutional psychoses showed essentially the same features as those in other psychoses; the degree of loss of emotionality on the whole was not so profound as in other disorders, but it was still pronounced. It is the impression of the author that psychoneurotic persons show a smaller loss of emotional responsiveness than psychotic patients and that all persons with organic disorders show the greatest diminution in emotionality.

WISE, Howard, R. I.

PSYCHIATRIC REPORT OF STUDY OF PSYCHOPATHIC INMATES OF A PENITENTIARY. CORNELIUS C. WHOLEY, J. Crim. Law & Criminol. **28**:52 (May-June) 1937.

Wholey reports the results of a comparative study of 239 psychopathic and 200 nonpsychopathic patients in a penitentiary. It was found that a larger percentage of the psychopathic than of the nonpsychopathic prisoners were single, that more of them were teetotalers and that a larger percentage of the psychopathic group came from homes in which either one or both parents were of foreign birth. Seventeen per cent of the psychopathic group were Negroes, as compared with 26 per cent of the nonpsychopathic group. The psychopathic prisoners showed greater instability in their work records. Twenty-one per cent of all crimes committed by psychopathic prisoners, and only 12 per cent of those committed by the nonpsychopathic prisoners, were murders. The psychopathic group committed their crimes at an earlier age than the nonpsychopathic group; 47 per cent, as compared with 34 per cent of the nonpsychopathic group, were under the age of 21 at the time of the first conviction. Seventy-one per cent of both the psychopathic and the nonpsychopathic group left home by the time they were 20; 36 per cent of the psychopathic, as compared with 27 per cent of the nonpsychopathic group, left home by the time they were 15. Thirty-three per cent of the psychopathic prisoners, as compared with 26 per cent of the nonpsychopathic, had three or more previous convictions. Thirty-eight per cent of the psychopathic group had an atypical score of more than 20 on the Woodworth psychoneurotic questionnaire, as compared with only 10 per cent of the nonpsychopathic group.

SELLING, Detroit.

REALITY AND THE UNCONSCIOUS. THOMAS M. FRENCH, Psychoanalyt. Quart. **6**:23, 1937.

There is in every one a constant tendency to revert to the wishes and emotional patterns of childhood and to irrational modes of thinking. This regression

fulfils the pleasure principle, but takes no account of the reality principle, by which present pain may be endured for the sake of an assured future pleasure. This type of future satisfaction is weak when pitted against immediate satisfaction. How is one able to renounce immediate pleasures, and even endure pain, for the hope of pleasure in the future? This is found in the nature of the unconscious. The unconscious is compelled to yield to wish-fulfilling tendencies and to the compulsion to relive painful experiences. The reality principle is not a modified form of the pleasure principle but a fortunate synthesis of the pleasure principle and the repetition impulses. The psyche, wishing to obtain pleasure, is compelled to come to terms with the memory of its mistakes and with their unhappy consequences; it makes a victim of necessity when it accepts a minimum of renunciation for the sake of future pleasure, in lieu of a merciless and futile compulsion to repeat its previous sufferings. It is because of the struggle between the unconscious urge for pleasure and the repetition of the unhappy consequences of these wishes that the urge to accept the reality principle ensues.

Intense psychic conflicts interfere with this step because the acceptance of reality requires the ability to learn, and acute conflicts not only make this new learning impossible but destroy discriminations which have been learned previously. The reality principle involves a modification of the pleasure-pain principle by taking account of future pleasures and pains, as well as a modification of the repetition compulsion to learning by taking account of the differential aspects of reality. Too great conflicts, as in the neurotic and the psychotic patient, absorb the psyche in the pain of the conflict and in vain attempts to wish it away. Learning is possible only when there is enough free energy at hand to make it possible to distinguish between the painful experiences of the past and the favorable aspects of the present. It is not the most painful elements in reality which the neurotic person ignores but those emotionally indifferent aspects the sole value of which is to serve as differential criteria in helping one to find new possibilities of gratification and in avoiding past mistakes.

PEARSON, Philadelphia.

DIAGNOSTIC VALUE OF DRAWINGS BY PROBLEM CHILDREN. T. TRAUBE, Arch. de psychol. **26**:285 (Dec.) 1937.

This study is based on the assumption that in drawing a child unconsciously gives a synthesis of his or her inner self. Traube studied a large number of drawings made by two groups of problem children. The interpretation of the drawings by the children in the first group was made by the author with the help of a personal interview with the child in each case, while the drawings by the subjects in the second group were interpreted independently and later verified by means of personal interviews. The results thus obtained, when compared with those for a group of normal children of the same ages, were found to be significant for the purposes of diagnosis.

GOBEY, Philadelphia.

PSYCHOMOTOR CORRELATIONS IN NORMAL SCHOOL CHILDREN. JADWIGA ABRAMSON and SUZANNE LE GARREC, Hyg. ment. **32**:1 (Jan.) 1937.

Abramson and Le Garrec attempted to correlate motor skill and the standard intelligence ratings of a number of normal school children. They found insufficient motor activity in pupils intellectually normal, superior or subnormal. They found also that pupils of superior intelligence often have inadequate motor skills.

ANDERSON, Los Angeles.

RESOLUTION OF THE CONCEPT OF PSYCHASTHENIA. A. AUSTREGESILO, Rev. de neurol. e psychiat. de São Paulo **3**:1, 1937.

The manifestations of psychasthenia, as characterized by Janet and Raymond, comprise: compulsive anxiety or motor acts; "psychologic insufficiency," or feel-

ings of physical incapacity; a sense of unreality; abulia; scruples, and hypochondria. Austregesilo believes that this group of disorders is heterogeneous in structure and course and that the cases of it are better classified under one or another of the following generally recognized headings: obsessive neurosis, usually accompanied by anxiety, fixed ideas, phobias or scruples; schizophrenia, in early or abortive stages, in which a "psychasthenic" or obsessive reaction is often observed; manic-depressive psychoses during the depressed stages of which obsessions may occur, and, occasionally, as equivalents in epilepsy.

PUTNAM, Boston.

THE RELATION BETWEEN MENTAL DISTURBANCES AND DISORDERS OF SPEECH: I. DISTURBANCES IN NAMING AND PARAPHASIA. E. STENGEL, Monatschr. f. Psychiat. u. Neurol. **95**:129 (April) 1937.

Stengel studied the effects of certain general mental alterations on the function of speech in a group of 6 patients suffering from cerebral vascular disease and post-traumatic and postepileptic mental disorders. All the patients showed disturbances of consciousness and an amnesic syndrome of the Korsakoff type, though confabulations were not as a rule prominent. Difficulty in naming objects, perseveration and paraphasic symptoms were observed in all the patients. Abstract problems were more difficult to solve than concrete ones. There was little spontaneous speech, but understanding of speech was not impaired. The difficulty in naming objects differed from that associated with amnesic aphasia, as the patients freely substituted incorrect names and seemed unaware of their errors. The patients often used names which had just been heard but which bore no relation to the object. Some mistakes owed their origin to perseveration; other faulty responses were characterized by the use of neologisms. The following types of paraphasic disturbances were distinguished: one, in which perseveration played a role; another, in which a tendency to flight of ideas was observed, and a third, in which confabulatory tendencies were noted. Mixtures of these three types were encountered in some cases.

From a descriptive point of view, the disorder of speech was regarded as an atypical aphasic disturbance, with the paraphasia placing it in the group of sensory aphasias. It was thought that the altered state of consciousness and the associated impairment of thought were largely responsible for the aphasic symptoms. A disorder of attention was probably the most important factor in producing the disturbance of thought. This explains the resemblance between the mistakes made by these patients and those observed in normal persons who were fatigued and inattentive. The general attitude of the patients toward speech also played a role in the aphasic symptoms. They were disinclined to talk or to use speech for the purpose of designating objects to which their attention was called. They showed a tendency to finish the task in the easiest and quickest manner possible, wishing to avoid the effort necessary to overcome their slowness of thought and impaired comprehension. The disorder of speech showed certain features which were reminiscent of the flight of ideas in manic states and of the neologisms observed in schizophrenia. From the attitude of the patients it was evident that their contact with the outside world was faulty. In this respect they resembled patients with schizophrenia. They tended to ignore the acquired knowledge of the relation between word and concept; as a result, their speech resembled that of children learning to talk. Further similarities to the speech of children were noted in the stubborn manner in which the patients defended their incorrect responses and in the frequency with which they echoed the words addressed to them. Stengel discusses the much disputed question whether aphasic conditions should be attributed to general psychic alterations or to disturbances of functions primarily concerned with speech. He believes that both these mechanisms are frequently operative, though there are extremes in which one or the other may be completely in the foreground.

ROTHSCHILD, Foxborough, Mass.

THE MIRROR SIGN. HELGE KNÖÖS, Acta psychiat. et neurol. **12**:155, 1937.

The mirror sign of Abély consists in the urge manifested by some patients with mental disease to take long and frequent looks at their own image in a reflecting surface, a window or a mirror. The face and body are the main objects of scrutiny. The sign is more frequent in men than in women, possibly because this behavior pattern is more apt to attract attention when displayed by men. Of 30 patients studied by Abély in which the sign was observed, 22 were schizophrenic. After schizophrenia, the sign was most frequently observed in persons with senile depression. The sign is considered to be an important warning symptom in the insidious and torpid forms of schizophrenia. It usually disappears when the disease becomes advanced, unless it persists as a manifestation of mere stereotyped mannerisms. Abély regards the symptom as a logical reaction to the feelings of change in the patient's own personality, as an expression of autism or as a manifestation of narcissistic homosexuality. Knöös believes that in some cases at least the mirror sign is a compulsive act.

YAKOVLEV, Waltham, Mass.

SIGNIFICANCE OF PREMATURE BIRTH IN THE DEVELOPMENT OF CEREBRAL DEFECTS, WITH ESPECIAL REFERENCE TO EXOGENOUS FACTORS CAUSING VARIOUS DEGREES OF MENTAL DEFICIENCY. T. BRANDER, Acta psychiat. et neurol. **12**:313, 1937.

The problem of mental development of the prematurely born infant is of practical importance. About 10 per cent of all newborn infants are premature, and about half of these, representing 5 per cent of all school children, survive to reach school age. Brander studied the intelligence quotient in relation to various endogenous and exogenous factors influencing the intellectual development of prematurely born infants, such as weight at birth, birth trauma and psychopathic heredity. His material consisted of 376 prematurely born children between 7 and 15 years of age. His findings were as follows: There is a definitely lower average intelligence quotient in the group of premature children than in a nonselected group of children of the same age. Birth trauma and psychopathic heredity tend to lower the intelligence quotient. The two factors in combination have an unfavorable effect at school age on the intelligence quotient of premature children. Psychopathic heredity alone has a more unfavorable effect than birth trauma alone. Thus, of a group of 230 premature children without birth trauma and without psychopathic heredity, 57.4 per cent were normal (intelligence quotient from 120 to 91), and 4.3 per cent were feebleminded (intelligence quotient 70 or below). Of a group of 66 premature children with complications at birth, 34.8 per cent were normal, and 13.6 per cent were feebleminded; of a group of 54 premature children with psychopathic heredity, 29.6 per cent were normal, and 24.1 per cent were feebleminded; of the group of 20 premature children with both birth trauma and psychopathic heredity, 30 per cent were normal, and 35 per cent were feebleminded. Study of the relation between weight at birth and the intelligence quotient in a group of 230 premature children without trauma at birth and without psychopathic heredity showed that the lower the weight at birth the lower the intelligence quotient at school age. The average weight at birth of 2,300 Gm. corresponded to an average intelligence quotient of 92; a weight of 2,200 Gm., to an intelligence quotient of 90; a weight of 1,900 Gm., to an intelligence quotient of 85, and a weight of 1,400 Gm., to an intelligence quotient of 77. Of complications at birth, face and breech presentations and precipitous delivery were most unfavorable. Low forceps delivery, asphyxia, moderate dystocia and protracted delivery seemed to have no influence on the intelligence quotient, but any combination of these complications was reflected immediately in a lower average intelligence quotient at school age. Trauma at birth has a more definitely unfavorable effect on the mental level of premature children than weight at birth alone. Breech presentation was asso-

ciated with a lower average intelligence quotient than normal delivery of infants of the same weight, and in the cases of breech presentation children delivered by version or by forceps showed a lower intelligence quotient than those of the same weight who were delivered without these procedures. As to the role of psychopathic heredity: Nonsyphilitic psychoses in antecedents showed no influence on the intelligence quotient. The occurrence of epilepsy was definitely unfavorable. Alcoholism was most unfavorable. Of a group of premature children with a history of alcoholism in the antecedents, 38.7 per cent were feebleminded. The author concludes that mental deficiency in the prematurely born infant is the result of the action on the nervous system of several endogenous and exogenous factors. Some of these factors are preventable, especially trauma at birth. Brander emphasizes the importance of prophylaxis at birth in preventing or reducing potential mental deficiency in the premature child.

YAKOVLEV, Waltham, Mass.

Diseases of the Brain

MILIARY ANEURISM OF THE ANTERIOR COMMUNICATING ARTERY. CYRIL B. COURVILLE and CLARENCE W. OLSEN, Bull. Los Angeles Neurol. Soc. **3**:1 (March) 1938.

Courville and Olsen report a series of 19 cases of aneurysm of the anterior communicating and adjacent arteries in a total of 47 cases of intracranial aneurysm. This relatively high proportion differs from that observed by other writers, who have reported a predominance of aneurysms in the posterior part of the circle of Willis. In 1 of the 19 cases an intact aneurysm had produced no symptoms and was an incidental observation at autopsy. Clinical analysis of the cases failed to reveal a consistent syndrome. Small unruptured aneurysms rarely produce symptoms but may involve the optic nerves, producing field defects. When rupture occurs, the location of the aneurysm, the direction of its growth and the exact site of rupture determine the characteristics of the lesions and the clinical manifestations. If the aneurysm is superficially located and breaks through its ventral wall little damage of the cerebral substance occurs, and the blood is poured into the subarachnoid space. On the other hand, when the aneurysm is deeply located between the frontal lobes the blood may penetrate into the white matter of one or both hemispheres and escape less readily into the basilar cisterns. In such cases symptoms of a "stroke" on one or both sides may initiate the clinical course, followed only subsequently by signs of meningeal irritation. In other cases the course of events may be reversed, with extensive hemorrhage into the subarachnoid space and secondary invasion of the brain. Rupture into one or both lateral ventricles almost invariably occurs if the hemorrhage is large. Massive hemorrhage into the ventricular system may force more blood through the sylvian aqueduct and fourth ventricle into the cisterna magna than escapes into the anterior fossa. Such ventricular hemorrhage may produce spasms of decerebrate rigidity, pupillary constriction, glycosuria, albuminuria, hyperthermia and early death. Rarely, one or both anterior cerebral arteries may be secondarily thrombosed after hemorrhage from an aneurysm of the anterior communicating artery. MACKAY, Chicago.

CARBON DISULFIDE POISONING: REPORT OF SIX CASES. S. T. GORDY and M. TRUMPER, J. A. M. A. **110**:1543 (May 7) 1938.

Gordy and Trumper draw attention to the fact that with the rapid growth of the rayon industry a health hazard has reappeared—carbon disulfide poisoning. Until the introduction of artificial silk, the rubber industry was the principal origin of carbon disulfide poisoning. There have been relatively few reports of cases of this disorder in America. The mode of entrance of carbon disulfide into the body is principally by inhalation of its vapor. Less frequently, it is absorbed by contact of the skin with the liquid, producing a sensation of burning followed by anesthesia. Prolonged contact produces second and third degree burns,

with blistering and local neuritis. Poisoning may occur in two forms: the acute and the chronic. The symptoms of acute poisoning are malaise, headache, vomiting, vasomotor disturbances, muscular cramps, motor unrest, excitement, unconsciousness and motor palsies. In chronic poisoning three syndromes may be differentiated, which frequently occur together: (1) somatic disorders, (2) organic disturbances of the central nervous system and (3) psychic disorders. The morbidity statistics from several large artificial silk factories indicate an incidence of gastric trouble of 17.7 per cent from exposure to carbon disulfide and hydrogen sulfide, while those from all other textile factories showed but 2.7 per cent. In the case of ulcers of the stomach and duodenum, the figures were 2.6 and 3 per cent, respectively. Prognosis depends on the age, the general bodily health and the promptness with which the poisoning is detected and the worker removed from the deleterious atmosphere. In many instances the somatic and neurologic disorders disappear after the worker is removed from exposure to the toxic agent. Brief exposure, however, may have long-continued or permanent sequelae. Tolerance is not established, or only rarely. On the contrary, there is an increased susceptibility to poisoning on further exposure. Women are more susceptible and show a greater incidence of psychic disorder. The psychosis may be permanent. In the 6 cases reported by the authors there was a relative paucity of neurologic signs. Two patients showed corneal anesthesia. Two patients complained of what might be termed "wavy vision"; 2 had retrobulbar neuritis, and 1 with an acute condition, lilliputian and brobdingnagian hallucinations (or illusions). As far as the authors are aware, "wavy vision" and this type of hallucination have heretofore not been reported in connection with carbon disulfide poisoning.

EDITOR'S ABSTRACT.

HEAD TRAUMA: REPORT OF 141 CASES. N. GOTTEN, J. A. M. A. **110**:1727 (May 21) 1938.

Gotten analyzes 141 consecutive cases of trauma to the head in which the patients were admitted to the neurological service at the Jewish Hospital, Philadelphia, from May 1933 to May 1936. The cases were classified by a rigid definition of head trauma; i. e., a period of unconsciousness of at least five minutes, a subarachnoid hemorrhage or fracture of the skull. There were 15 deaths. There were 60 patients under 20 years of age, 66 between 20 and 60 and 15 over 60. The mortality rate was 5 per cent in the first group, 10.6 per cent in the second group and 33.3 per cent in the group over 60 years of age. In a review of the data from the standpoint of the decade of life in which the injury occurred, the following deductions may be made: If a patient is under 20 years of age he has approximately a 20:1 chance of recovery from injury to the head. If he is between the ages of 20 and 60, his chances of recovery are reduced to 10:1, whereas if he is over 60 his chances are only 3:1. These figures are not related to the severity of the injury. Complications secondary to the injury were the chief factors causing death in the aged. Of the 141 patients, 7 underwent operations. Of these, 4 recovered and 3 died. Three children with depressed fractures recovered completely after decompression and removal of fragments of bone. One patient with a traumatic aneurysm of the internal carotid artery recovered after ligation of the common carotid artery. The condition in the 3 remaining patients was diagnosed as mass hemorrhage. In 2 of these instances a blood clot was observed and removed, while in the other case severe contusion of the brain was demonstrated at operation. No distinction should be made between cases in which the skull is fractured and those in which blood is seen in the cerebrospinal fluid. These conditions are only an index to the severity of injury the brain has received. Neither fracture of the skull nor a subarachnoid hemorrhage alone can be used as the criterion of injury to the head. Either of these manifestations of brain trauma is sufficient to warrant hospital or bed care. Many patients, after a severe blow to the head, have neither of these two manifestations but show symptoms of trauma to the central nervous system. It is probable that all cases in which

a period of unconsciousness exists should be classified under the one term "brain contusion." Inability of the physician to find the clinical manifestations does not remove the underlying pathologic condition. Particular attention should be given to patients presenting on first examination evidence of very mild cerebral injuries. Subsequent examinations have shown that mild trauma frequently brings on serious complications in both young and old patients. These complications are manifested by convulsions, transitory paralysis, aphasia, severe vertigo, persistent headache and the like. The pathologic basis for these observations is probably multiple petechial hemorrhages throughout the entire brain. Conservatism in treatment is important. The patient is given preliminary treatment for shock and then a thorough neurologic examination. Lumbar punctures are done routinely only to relieve any increase in intracranial pressure. Hypertonic solution of dextrose is not advocated. The only conditions requiring operation are subdural and epidural hemorrhages and those of compound or depressed fractures.

EDITOR'S ABSTRACT.

PRIMARY FIBROBLASTIC TUMORS OF THE CHOROID PLEXUS OF THE LATERAL VENTRICLES: CLINICOPATHOLOGIC STUDY OF THREE CASES. W. J. GARDNER and O. A. TURNER, Surg., Gynec. & Obst. **66**:804 (April) 1938.

Gardner and Turner present 3 cases of primary fibroblastoma of the choroid plexus of the lateral ventricle. All 3 tumors were removed at operation. In each case, the intraventricular location of the tumor was not suspected from the clinical signs, and the exact localization was made only at operation. The tumors were of mesodermal origin and probably arose from the fibrous elements of the choroid plexus or tela choroidea. There is no clinical picture that will localize an intraventricular growth, although there are certain neurologic features which may at times direct attention to the possibility of a lesion in this location. This is particularly true when localizing signs are absent in the presence of an obviously expanding intracranial lesion. Periodic headaches or intermittent attacks of increased intracranial pressure have both been cited as the most suggestive evidence of a growth within the lateral ventricle. This periodicity is due to the ball valve action of the tumor and can occur in other parts of the ventricular system, namely, in the third ventricle. When the large size of the tumor prevents it from moving freely or when local adhesions fix the tumor in one position, this phenomenon may be absent. Obvious signs of increased intracranial pressure may be late in developing in young patients, since in them separation of cranial sutures may serve to decompress the brain until the bulk of the tumor plus the concomitant cerebral edema overcomes this compensation. Hemianesthesia and hemiplegia have been pointed out as the most important localizing evidence. Intraventricular tumors appear to occur most frequently during the first three decades of life. While in many instances the symptoms are less than one year in duration, there are wide variations. In tumors in this location, the duration of symptoms is not an index of the malignant condition of the growth, since, by reason of their location, they may block circulation of the cerebrospinal fluid and produce fulminating signs of increased intracranial pressure, despite the fact that they may be encapsulated and benign.

EDITOR'S ABSTRACT.

SUPRACALLOSAL EPIDERMOID CHOLESTEATOMATA. A. R. D. PATTISON, Lancet **2**: 1303 (Dec. 4) 1937.

Since epidermoid cholesteatoma in the region of the corpus callosum has never been reported, 2 cases are described, 1 in a man aged 29 and the other in a woman aged 25. In both instances the insidious development of the symptoms and the transient nature of the signs led to the erroneous diagnosis of multiple sclerosis. This was probably due to the slow enlargement of the neoplasm and to a "toxic substance elaborated by the tumor." In both patients convulsions played a prominent role. One died after prolonged status epilepticus; in the other permanent left

hemiplegia developed after an operation and status epilepticus during convalescence. Colloidal thorium dioxide injected into the left lateral ventricle revealed a mass over the intermediate portion of the corpus callosum. After operation the patient had a temperature of 103 and 104 F., which persisted for five months. Striking improvement was then noted, but suddenly, twenty-one weeks after the operation, status epilepticus occurred. Recovery took place after ten days of coma, with residual left hemiplegia. Cholesteatomas are of congenital origin and occur where primary flexures of the embryonic brain are manifest. The supracallosal location of the tumors is perhaps attributable to epithelial implantation when the vesicles of the forebrain expand and approximate one another. KRINSKY, Boston.

REFLEX EPILEPSY. A. RADOVICI, M. SCHACHTER and S. KISILEV, Encéphale **2**:26, 1937.

The authors report 7 cases of reflex epilepsy. In 2 cases a single seizure occurred in patients who had taken monobromated camphor for urethritis and who never had fits previously. No new fits occurred in a period of observation of six and two years, respectively. In a third case the patient, who had seizures with a sensory aura in the foot, could prevent the onset of a fit by compressing the foot. In 2 other cases epilepsy followed a bullet wound in the abdomen and a depressed fracture of the skull, respectively, with seizures provoked by noise, and in 2 cases attacks were provoked by exposure to sunlight. The peripheral stimulation resulting in reflex epileptic seizures is often of normal intensity. The nerve cells probably transmit the stimuli abnormally, and this constitutes a predisposition to reflex epilepsy. LIBER, New York.

INTRAVENTRICULAR MENINGIOMA. M. DAVID, L. GUILLAUMAT and H. ASKÉNASY, Rev. neurol. **67**:504, 1937.

Tumors arising within the lateral ventricles are not frequent. Most of them are either epithelial tumors of the choroid plexus or ependymal gliomas. Meningiomas are uncommon, and their operative removal is rare. The authors report a case in which an intraventricular meningioma was successfully removed. A man aged 36 had five years before first experienced constrictive bilateral frontal headache. The headaches were intermittent and increased with movement. After four years vision began to diminish, and shortly afterward increasing paresis of the right leg and attacks of sensory aphasia developed. Finally, the right upper extremity became paralyzed and anesthetic, and astereognosis appeared. There were slight papilledema on the left side and pallor of the disk on the right. Ventriculographic examination showed that the left occipital horn was narrow and deviated to the right. The atrium ventriculi and the posterior portions of the body of the ventricle and the temporal horn on the left were obliterated. Operation revealed an intraventricular tumor attached by numerous blood vessels to the choroid plexus and the tissue of the hemisphere. The growth weighed 120 Gm.; it was removed in one piece. The bone flap was replaced. On the tenth day after operation hemiplegia and, soon afterward, aphasia began to regress. After seven weeks the patient left the hospital in excellent state. Histologic examination of the tumor, by del Rio-Hortega, showed it to be a lamellar meningioma.

LIBER, New York.

ANATOMIC BASIS OF THALAMIC SYNDROMES. A. E. WALKER, J. belge de neurol. et de psychiat. **38**:69 (Feb.) 1938.

The spinothalamic tract and its trigeminal equivalent, the dorsal secondary trigeminal tract, terminate in the basal posterior portion of the lateral nuclear mass of the thalamus in a specific fashion. The fibers from the spinal root of the trigeminal nerve terminate medially, those from the sacral portions of the

spinal cord laterally and those from the cervical regions in the intermediate portion. The medial lemiscus and the ventral secondary trigeminal tract end more dorsally and anteriorly in the ventral portion of the lateral nuclear mass with precisely the same topical arrangement. The fibers from the superior cerebellar peduncle arborize in the anterior half of the lateral nuclear mass, oral and dorsal to the termination of the lemnisci. The topical arrangement of the afferent systems within the thalamus finds an anatomic correlate in the organization of the thalamocortical projection. The anterior half of the lateral nuclear mass, in which the fibers from the brachium conjunctivum arborize, sends its axons to the motor and premotor areas of the cerebral cortex. The ventral portion of the posterior moiety of the lateral nuclear mass, which receives the terminations of the spinothalamic and lemniscal tracts, projects exclusively to the postcentral convolution. The two projections have a similar topical organization. The fibers which arise in the medial portion of the lateral nuclear mass terminate in the inferior parts of the precentral and postcentral gyri, those from the lateral part in the superior portion of these convolutions and those from the intermediate part in the middle portion. Thus, there is maintained throughout the entire sensory system a precise organization of the body segments.

The classic thalamic syndrome is the result of a lesion of the posterior portion of the lateral nuclear mass, which causes severe sensory disturbances by involvement of the part of the thalamus in which the spinothalamic and lemniscal tracts terminate. The dissociation of sensation is probably dependent on the numerous other connections (with the pons, mesencephalon and midbrain) made by the spinothalamic system. Lesions of the anterior portion of the thalamus, usually due to thrombosis of the perforating thalamic artery, produce few sensory disturbances; they cause tremor, ataxia and choreoathetoid movements of the contralateral extremities. These lesions involve the part of the thalamus in which the fibers of the brachium conjunctivum find their termination. Hence, it is not surprising that a lesion in this region produces signs and symptoms which are usually associated with cerebellar disease. Occasionally small lesions of the thalamus are present, displaying only a fragment of the aforementioned syndromes.

DE JONG, Ann Arbor, Mich.

NOTES ON ENCEPHALITIS IN SHANGHAI. RICHARD D. LÖWENBERG, Chinese M. J. **51**:989 (June) 1937.

Contrary to general belief, most of the various forms of neurotropic virus infection of the central nervous system occur sporadically in Shanghai, China. Löwenberg describes the various types of nonpurulent encephalitis encountered in Shanghai. One type is most conspicuous: Abrupt onset during the late summer, without any other preliminary infection; grave cerebral symptoms, especially paresis of the eighth nerve, but seldom ophthalmoplegia; absence of new symptoms several months after the onset, and rapid recovery without essential sequelae are characteristic features. This special form of encephalitis is neither of the lethargic nor of the postinfectious type, the so-called encephalomyelitis disseminata. Nor is it to be confused with other forms, such as the cerebral forms of poliomyelitis or of meningitis aseptica. There are clear clinical and epidemiologic indications that the disease in these cases may be connected with Japanese B encephalitis and the St. Louis form, so that a tentative classification with this group may be justified. At present one can find only sporadic cases, but there is every reason to believe that the disease is not rare among the population of Shanghai.

AUTHOR'S ABSTRACT.

MISLEADING SYMPTOMS IN A CASE OF GLIOMA OF THE FRONTAL LOBE. H. GANNER, Arch. f. Psychiat. **106**:436 (April) 1937.

Ganner reports the case of a man aged 55 with a glioblastoma multiforme in the white matter of the left frontal lobe. During eight months a series of symp-

toms developed which tended to interfere with proper localization. These consisted in disturbances of upward movements of the eyes, vertical nystagmus, changeable pupillary inequality and double vision. All pointed to a lesion of the midbrain. An encephalogram showed a filling defect of the left lateral ventricle, which was considered indicative of either an intraventricular tumor or occlusion of the foramen of Monro. The latter had to be excluded because the left lateral ventricle could not be reached, even by the ventriculographic procedure. This led to the proper diagnosis, which was followed by surgical intervention. The author stresses the importance of keeping in mind the possible effects of remote pressure.

MALAMUD, Iowa City.

SPASMODIC TORTICOLLIS. MARCEL MONNIER, Schweiz. Arch. f. Neurol. u. Psychiat. **40**:345, 1938.

Of the 6 cases of spasmodic torticollis studied, the condition was apparently of psychic origin in 4; in the other 2 it was associated, respectively, with facial paraspasm and hemihypertonia and with multiple sclerosis. The torticollis was relieved when the patients assumed reclining positions, especially the dorsal decubitus, and was worse when they were standing erect or sitting. The condition was alleviated by extension of the head, upward gaze and deviation of the eyes toward the side of the spasm. Elevation of the arm on the side opposite that of the spasm was likewise effective, as were certain automatic and rhythmic movements, such as rapid walking and swimming. The acts of yawning, eating, drinking, singing and crying also diminished the spasm. Application of light friction or a vibrating tuning fork to the side of the neck opposite the spasm had a favorable effect; warmth decreased and cold increased the spasm. Either occlusion or exposure of the eyes to green light, particularly the eye on the side opposite the spasm, was helpful, whereas exposure to red light had the reverse effect. Loud discordant sounds, even music of the blaring or "jazz band" variety, made the spasm worse. Silence, melodious tunes and the deep notes of the cello, on the other hand, were beneficial. Some of the patients were better when moving rapidly in an automobile, motorcycle or public conveyance. Unpleasant emotions aggravated the condition; diversions which promoted a state of euphoria proved helpful. The spasms disappeared entirely during sleep; they were less marked during digestion, and at times during menstruation. Local therapeutic measures, such as warm applications and intramuscular injections of sodium iodide reduced the spasm.

Chronaxia of the sternocleidomastoid and trapezius muscles was found to be normal on the side of the spasm and increased, usually from two to four but occasionally eight or nine times, on the opposite side. This indicated that torticollis is due to a decrease of neuromuscular activity on the apparently normal side of the neck, the assumed hypertonia of the contracted muscles being relative. Vestibular studies of the 2 patients whose spasms were relieved by exposure of the opposite eye to green light showed in both instances hypoexcitability of the labyrinth on the side of the spasm. Monnier believes that both the frontal lobes and the cerebellovestibular system play a part in the maintenance of equilibrium in the activity of the muscles of the neck and, consequently, in the pathogenesis of spasmodic torticollis.

DANIELS, Denver.

Diseases of the Spinal Cord

COMPRESSION OF THE SPINAL CORD IN THE NEIGHBOURHOOD OF THE FORAMEN MAGNUM. C. P. SYMONDS and S. P. MEADOWS, Brain **60**:52, 1937.

The clinical picture which results from compression of the spinal cord at or near the level of the foramen magnum is not always easy of recognition. In particular, the distinction from intramedullary disease, tumor or syringomyelia may be difficult. Elsberg (1924), in a monograph on tumors of the spinal cord, reported 2 cases of compression at high cervical levels, in 1, from a dermoid cyst, and in

the other, from an aneurysm of the right vertebral artery. He laid stress on the following points: Pain in the neck and occipital region is an important symptom and is increased on movement of the head. The patient is therefore apt to hold the head stiffly. Weakness first appears in the ipsilateral upper limb and is soon followed by subjective and objective sensory disturbances in the same limb. Weakness in the other limbs usually appears in regular sequence, affecting first the ipsilateral and then the contralateral lower limb and, finally, the contralateral upper limb. Elsberg and Strauss (1929) again emphasized the importance of pain and rigidity in the neck and observed as a striking feature the occurrence of dissociation in the cutaneous sensory loss of the syringomyelic type. They added that the complaint of cold in one or both lower limbs, usually in the contralateral limb, is a common subjective symptom, which they had encountered only in cases of high cervical tumor. They noted also the occurrence of atrophy in the muscles of the forearm and hand in cases of extramedullary tumor confined to the upper three cervical segments.

In this communication, Symonds and Meadows report 7 cases of compression of the spinal cord in the region of the foramen magnum. The compression in 2 cases was caused by an aneurysm of the right vertebral artery and an atlanto-axial dislocation, respectively, and in each of the other 5 cases by a benign tumor, either an endothelioma or a neurofibroma.

Involvement of the cranial nerves is not usually observed in these cases unless a large part of the tumor is above the foramen magnum. In 1 case the authors observed severe involvement of the spinal accessory and hypoglossal nerves, with some impairment of sensation in the trigeminal field. In this case the compression was caused by an aneurysm of the vertebral artery, the level of the compression being above the level of the foramen magnum and only a small portion of the tumor extending below it. Cervical sympathetic palsy seems to be an inconstant phenomenon in this syndrome. Some evidence of cervical sympathetic palsy was evident in 4 cases. In all 7 cases spastic weakness of the limbs was prominent. This involvement of the limbs follows the order described by Elsberg (1924). Localized muscular wasting was present in 5 cases. The wasting involved the intrinsic musculature of the ipsilateral hand and was a striking feature. In 1 of these cases there was generalized wasting of both upper limbs. The occurrence of atrophy in the hand as the result of a lesion at a level higher in the cervical portion of the cord than that for innervation of the small muscles of the hand may be due to interference with a descending arterial supply to the motor cells concerned. As a fact of clinical observation the point is clearly of great importance, for misinterpretation may easily lead to a diagnosis of syringomyelia. Paralysis of the diaphragm occurred in 1 case in association with an earlier history of hiccup.

Of great clinical importance is the fact that in each of the 7 cases subjective pain or paresthesia was an early symptom; in each case this symptom first appeared in the upper limb first affected by spastic weakness. The sensory symptoms clearly cannot be attributed to pressure by the tumor on appropriate roots but must be due to interference with an intramedullary pathway, probably the posterior column. The practical importance of this combination of symptoms lies in the fact that the history of progressive numbness and weakness of hemiplegic distribution may easily suggest a diagnosis of cerebral rather than of spinal tumor.

Elsberg and Strauss (1924) have emphasized the dissociated character of the cutaneous sensory defect. A severe degree of loss of sensation to painful and thermal stimuli may be associated with a normal response to tactile stimuli as judged by clinical standards. Furthermore, there may be dissociation in the response not only to heat and cold but to thermal and other kinds of pain. These observations are confirmed in every point by the authors' study. Practically, the recognition of the occurrence of such dissociated anesthesia in cases of high cervical tumors is of importance in the differential diagnosis of this condition and syringomyelia.

In each of 5 cases in which the tumor was laterally placed there was some sensory defect on the side of the lesion. In several cases a bilateral sensory defect in the upper cervical segments was observed. The simplest explanation for the latter fact is that there is impairment of conduction at the level of compression not only in the spinothalamic fibers but in those of the zone of entry of the roots on both sides.

Sensory defect of the type which depends on interference with the posterior columns was a conspicuous feature in 6 cases. From an analysis of the location of the tumor the authors conclude that in cases of compression at this level the time of onset of involvement of the posterior columns depends on the degree of compression of the spinal cord rather than on the site of incidence of the compression in relation to the circumference of the cord. This view is in agreement with that of Elsberg (1925), who stated that as a rule disturbances in vibratory and articular sense in cases of spinal tumors always occur when the pressure has affected the entire thickness of the cord, whether the growth is ventrally or dorsally placed.

Impaired sphincter control was present in only 1 case. Some abnormality of the cervical portion of the spine was found on clinical examination in every case, but in no instance was this striking. In only 2 cases were the response to the Queckenstedt test negative and the protein content of the spinal fluid within normal limits. These were the 2 cases in which the compression was not due to a tumor. Roentgenographic examination failed to reveal abnormality of the cervical portion of the spine in any case. Cisternal puncture at this level for the purpose of injection of iodized poppyseed oil is probably a dangerous procedure and is unlikely to give successful results. It failed in 2 cases. Injection by the lumbar route and examination on a tilting table were attempted in 4 cases. The authors conclude that with the body in the reversed position arrest of the iodized oil in the upper cervical region, unless it reveals the convex outline of a tumor, is not to be relied on as a guide to localization.

SALL, Philadelphia.

SPONTANEOUS HAEMATOMYELIA. J. M. HOLMES, Brit. M. J. **1**:946 (April 30) 1938.

Holmes reports the case of a girl aged 15 who experienced a sudden severe pain in the back and legs. Within a few minutes the legs were paralyzed and numb. Examination disclosed flaccid paraplegia with anesthesia below the fifth dorsal level. The spinal fluid was bloody and under a pressure of 290 mm. of water. There was no spinal block and no history of recent illness, injury or unusual exertion. On the fourth day of the illness the level of sensory loss had risen to the second dorsal segment, and there was respiratory distress. Artificial respiration was required for ten days. Gradual improvement followed; when examined eleven months later the patient was able to walk. Full sensation had returned, but the legs were still spastic. Holmes concludes that the patient probably had hematomyelia as a result of spontaneous rupture of a spinal hemangioma.

ECHOLS, New Orleans.

ACUTE EPIDURAL ABSCESS. W. R. D. MITCHELL, Brit. M. J. **1**:1149 (May 28) 1938.

A review of the reported cases of acute epidural abscess shows no instance of recovery without surgical intervention. In only a few instances has complete recovery followed surgical therapy. The organism in the cases reported has been Staphylococcus albus or Staphylococcus aureus. Epidural abscess may result from extension from a neighboring area of infection, or it may be metastatic. The diagnosis can be made when there are pain over the spine, progressive paraplegia and evidence of an acute infection. The only treatment is adequate drainage by laminectomy. Mitchell reports a case in which there was complete recovery from paraplegia after drainage of an epidural abscess at the level of the third lumbar vertebra.

ECHOLS, New Orleans.

CRYPTOGENETIC INFLAMMATORY EPIDURITIS, WITH MEDULLARY COMPRESSION AND PARAPLEGIA. J. A. CHAVANY, M. DAVID and L. STUHL, Rev. neurol. **67:** 499, 1937.

The authors report the case of a woman aged 35 who began to suffer from intense pains in the lumbar and sacroiliac regions in 1931. Two years later the pains spread to the anterior regions of the thighs and were followed by spastic paraplegia. There were slight sphincter disturbances and loss of libido. No objective sensory disturbances were found. The protein content of the spinal fluid was 0.6 Gm. per liter. There was no subarachnoid block. The condition progressed, so that one year later hypesthesia appeared; the spinal fluid contained 25 lymphocytes per cubic millimeter and 0.5 Gm. of protein per liter; there was complete lumbar block. Injection of iodized poppyseed oil showed a block between the twelfth thoracic and the first lumbar vertebra. At operation an extradural fibrous mass extending from the tenth thoracic to the lower border of the first lumbar vertebra was dissected away. It proved to be of dense fibrous tissue with fatty areolar areas containing lymphocytes and mononuclear cells. Marked improvement followed, but the symptoms reappeared after eight months. A second operation revealed a circular band outside the dura. This was removed completely, together with portions previously left behind. Postoperative improvement has persisted.

LIBER, New York.

UNILATERAL SYNDROME OF THE CONUS MEDULLARIS DUE TO HEMATOMYELIA. EGAZ MONIZ and LUIZ PACHECO, Rev. neurol. **67:**575, 1937.

Egaz Moniz and Pacheco report 2 clinical cases of a unilateral syndrome of the conus medullaris. Case 1 was that of a man aged 46 with recurrent articular rheumatism. A sudden, intense pain in the left hip was followed by numbness and tingling in the left leg, left foot drop, diminution of erection and delayed ejaculation. The left ankle jerk was absent. Pain and temperature sensations were greatly diminished in all sacral sensory areas, and that of touch was slightly decreased. Roentgenograms of the vertebrae and examination of the spinal fluid revealed nothing abnormal. The Wassermann reaction of the blood was negative. Case 2 was that of a man aged 73, who noticed that the left foot dragged and could not be flexed after defecation. Slight weakness of the right leg disappeared rapidly. There were no pains, paresthesias or sphincter disturbances. Genital dysfunction could not be estimated because of the patient's age. Perception of pain and temperature was diminished in the left sacral territories and slightly in the fourth and fifth lumbar areas. Some improvement followed a month and a half of symptomatic treatment. There was no muscular atrophy in either case. The unilateral involvement of several superposed segments could be explained only by an intramedullary hemorrhage which spread vertically.

LIBER, New York.

FOUR CASES OF FRIEDREICH'S ATAXIA, WITH A STUDY OF THE FAMILY HISTORY. FRIEDRICH ROLLE, Deutsche Ztschr. f. Nervenh. **144:**38, 1937.

Rolle reports 4 cases of Friedreich's ataxia, in 1 of which the disease was complicated by schizophrenia. The family history was studied in detail for from three to five generations. In each case there was sporadic occurrence of the disease. Rolle was impressed with the frequency of the occurrence of status dysraphicus in other members of the family.

MERRITT, Boston.

Cerebrospinal Fluid

VITAMIN C IN BLOOD, SPINAL FLUID AND URINE. H. WORTIS, J. LIEBMANN and E. WORTIS, J. A. M. A. **110:**1896 (June 4) 1938.

Wortis, Liebmann and Wortis determined in 133 patients the vitamin C content of the blood, the spinal fluid and the five hour specimen of urine after an intra-

venous test dose of 1 Gm. of cevitamic acid. A vitamin C content of the blood above 0.7 mg. per hundred cubic centimeters (by the method of Farmer and Abt) is almost invariably associated with a normal spinal fluid content and a normal value for the urinary excretion test. A blood content below 0.4 mg. per hundred cubic centimeters is almost invariably associated with a subnormal spinal fluid content and a subnormal value for the urinary excretion test. In these ranges the blood is an adequate and accurate index of the state of vitamin C nutrition. For patients showing the intermediate subnormal range of values for blood (from 0.4 to 0.69 mg. per hundred cubic centimeters), all available tests should be used, including clinical evaluation. Scurvy is a clinical entity, and its diagnosis cannot be made by vitamin C determinations alone. In studies of excretion of vitamin C in the urine, the authors' results showed that a subnormal value for the five hour excretion test is almost invariably associated with subnormal values for the blood and the spinal fluid. A normal value in the excretion test is almost invariably associated with a normal value for the spinal fluid and a value for the blood above 0.4 mg. per hundred cubic centimeters. When the vitamin C content of the spinal fluid was determined, the authors' results showed that a subnormal value (i. e., below 1.82 mg. per hundred cubic centimeters) is almost invariably associated with a subnormal value for the blood and in the urinary excretion test. A normal value for the spinal fluid may be associated with either normal or subnormal values for the blood and the urine.

EDITOR'S ABSTRACT.

THE EFFECT OF PITRESSIN AND WATER INTAKE ON THE CEREBROSPINAL FLUID. J. N. CUMINGS and N. S. ALCOCK, J. Neurol. & Psychiat. **1**:61 (April) 1938.

Cumings and Alcock investigated the behavior of the cerebrospinal fluid in relation to dilution of the blood by oral administration of large quantities of water after a preliminary subcutaneous injection of solution of posterior pituitary. Four groups of fluid were examined: (1) the lumbar cerebrospinal fluid from 7 normal subjects; (2) the ventricular fluid from 2 normal subjects; (3) lumbar cerebrospinal fluid obtained from below a spinal block in 3 patients with spinal lesions, and (4) hydrocele fluid and blood from 2 subjects. The ratio of dilution was estimated by measuring the concentration of hemoglobin, sugar, urea, calcium, inorganic phosphorus, magnesium and chlorides in the various fluids and was expressed in accordance with Donnan's theory. The following results were obtained: In group 4 the hydrocele fluid was diluted in a ratio similar to that occurring in the blood, indicating that the mechanism of dilution was one of dialysis. In groups 1 and 2 there was an irregular dilution of the cerebrospinal fluid, and in certain instances some of the constituents showed an increased concentration. In group 3 the cerebrospinal fluid showed little or no dilution. This suggested that the mechanism for the formation and absorption of the cerebrospinal fluid is not one of simple dialysis, but is to be attributed either to an active secretory or selective filtration process in the choroid plexus or to a selective and varying rate of absorption of the individual constituents of the cerebrospinal fluid.

MALAMUD, Ann Arbor, Mich.

LUMBAR PUNCTURE PRESSURES IN SUBARACHNOID HEMORRHAGE. R. KEMP, Lancet **2**:1369 (Dec. 11) 1937.

Few reports of cases of subarachnoid hemorrhage are available in which lumbar puncture pressures have been recorded. Kemp analyzes the spinal fluid pressure in 9 cases of subarachnoid hemorrhage, in 6 of which the patients recovered. In each case the spinal fluid pressures were not elevated during the early stages. After one week the pressures in 2 cases were over 200 mm. of water. In 4 cases the spinal fluid levels were low.

KRINSKY, Boston.

CEVITAMIC ACID CONTENT OF CEREBROSPINAL FLUID OF HUMAN SUBJECTS. J. MĚLKA and Z. KLIMO, Klin. Wchnschr. **17**:302 (Feb. 26) 1938.

Mělka and Klimo say that efforts to utilize deviations in the cevitamic acid content of the cerebrospinal fluid as a diagnostic aid in diseases of the central nervous system have failed. On the other hand, low cevitamic acid content of the cerebrospinal fluid is a manifestation of C hypovitaminosis. The authors studied the cevitamic acid content of the cerebrospinal fluid for an entire year in order to estimate the influence exerted by the food during the different seasons. They made systematic studies for thirteen successive months on 277 subjects. Some of the specimens of cerebrospinal fluid were from normal subjects, and some were from patients with disorders of the central nervous system. Since in both groups the values were often low and normal values were often found in patients with severe disorders of the central nervous system, it was concluded that the detected values were of no diagnostic significance. However, there were seasonal fluctuations of the cevitamic acid content of the cerebrospinal fluid. The minimum was detected during the spring months, and the maximum, during the fall. The authors conclude that the cevitamic acid content of the cerebrospinal fluid is an important diagnostic aid in the diagnosis of hypovitaminosis. EDITOR'S ABSTRACT.

DIFFERENTIAL PRESSURE OF CEREBROSPINAL FLUID IN CASES OF CEREBRAL TRAUMATISM. P. DECKER, Schweiz. med. Wchnschr. **68**:588 (May 21) 1938.

Decker discusses the possible causes of the increase in intracranial tension after cerebral traumatisms and the treatments that aim at dehydration of the brain. He points out that this method is not without danger, for if continued too long it may give rise to the phenomenon of so-called toxic dehydration. Consequently, it is important to know when to suspend the dehydration. The author found that his method of determination of the differential pressure of the cerebrospinal fluid is of value in this respect. He measures the pressure of the cerebrospinal fluid at the beginning and at the end of lumbar puncture, during which a definite amount (perhaps 1 cc. of fluid) is extracted. In 1 case of commotio cerebri the pressure at the beginning of the lumbar puncture was 22 cm.; after the extraction of 1 cc. of fluid it was 17 cm., and after the extraction of 2 cc. it was 13 cm. Thus, the differential pressure per cubic centimeter was 4.5 cm. Repeated lumbar punctures revealed that this differential pressure subsided gradually. The author gained the impression in a number of cases that the differential pressure in cerebral traumatism is related to the variations in the cerebral volume, which are the result of the edema. He thinks that the study of the differential cerebrospinal pressure can aid in directing the treatment of post-traumatic cerebral disturbances, particularly if the treatment consists in dehydration. EDITOR'S ABSTRACT.

FURTHER INVESTIGATIONS INTO THE DIASTASE CONTENT OF THE VENTRICULOSUBARACHNOID SPACE. H. CHRISTIANSEN, Acta psychiat. et neurol. **12**:599, 1937.

Christiansen's studies have shown that in 80 per cent of cases the diastase content of the cerebrospinal fluid represents from 1 to 5 per cent of that of the blood serum. In only 2 per cent of cases was the diastase content less than 1 per cent of that of the blood serum. In the present study, Christiansen reports the results of determinations of diastase in the cisternal, lumbar and ventricular fluids. Simultaneous determinations of diastase in the blood serum and in the cisternal and lumbar fluids of 2 alcoholic patients showed that the cisternal fluid contained slightly less diastase than the lumbar fluid. The results of the determinations of diastase in 35 samples of ventricular fluid show that the ratio of diastase in the serum to that in the ventricular fluid is less than 1 per cent. Also, the absolute concentration of diastase is low. The diastase content of the cerebrospinal fluid

increases caudally. This is explained by the fact that diastase is composed of large molecules, approaching in size the molecules of protein. Thus, its concentration in the ventriculosubarachnoid fluid is similar to that of proteins.

YAKOVLEV, Waltham, Mass.

Treatment, Neurosurgery

THE EFFECT OF SPLANCHNIC NERVE RESECTION ON PATIENTS SUFFERING FROM HYPERTENSION. IRVING H. PAGE and GEORGE J. HEUER, Am. J. M. Sc. **193**: 820 (June) 1937.

Resection of splanchnic nerves with interruption of the thoracic portion of the sympathetic chain was performed on 9 patients. The operation consisted of the bilateral resection of segments of the great, small and smallest splanchnic nerves, together with the three lower dorsal ganglia. Six patients, ranging in age from 25 to 48 years, had mild or severe essential hypertension. The operation was followed by marked reduction in arterial pressure, but within six months the pressure had returned to the preoperative level in all the patients. Renal efficiency was not affected by the operation. Reduction in the intensity of constriction of the retinal arterioles occurred, but in most of the patients it returned after several months. The therapeutic results in this series of patients were not encouraging.

MICHAELS, Boston.

SYMPTOMATIC TREATMENT OF CHRONIC ENCEPHALITIS WITH BENZEDRINE SULPHATE. ROBERT A. MATTHEWS, Am. J. M. Sc. **195**:448 (April) 1938.

Matthews treated 20 patients with the postencephalitic parkinsonian syndrome with benzedrine sulfate, 18 of whom have been receiving the drug by mouth for from six to twelve months. Fifteen (75 per cent) showed definite sustained improvement; the symptoms beneficially affected were rigidity, tremor, salivation and oculogyric crises. There were improvement in mood and an increase of strength and energy. In no instance were there untoward effects necessitating discontinuance of the drug. The results of the study have been encouraging and warrant further investigation.

MICHAELS, Boston.

REVIEW OF RESULTS FROM EMPLOYMENT OF MALARIA THERAPY IN TREATMENT OF NEUROSYPHILIS IN THE FLORIDA STATE HOSPITAL. M. F. BOYD, W. K. STRATMAN-THOMAS, S. F. KITCHEN and W. H. KUPPER, Am. J. Psychiat. **94**:1099 (March) 1938.

Boyd and his associates compare the late results of malarial therapy supplemented with chemotherapy in 190 cases of cerebrospinal syphilis with those of chemotherapy alone in 20 concurrent cases. Of the patients receiving malarial therapy, 55 per cent showed improvement or complete remission, as compared with 30 per cent of those receiving chemotherapy alone. The quartan parasite appears to be the most effective agent for producing the requisite number of severe paroxysms. The best results were secured from the application of malarial therapy to persons less than 30 years of age. Such patients react favorably to fewer paroxysms than appear necessary to produce comparable results in older persons. Better results were secured in the asymptomatic than symptomatic form. Of the latter, in the cases in which there were only organic signs better results were given than in those in which mental involvement existed. The severity of the paroxysms experienced, rather than their number, appears to have a definite influence on the results secured. It is suggested that the objective of malarial therapy should be the subjection of the patient to a minimum of twenty-one paroxysms which attain a height of 104 F. or more and that, if the first strain or

species of parasite employed fails to produce this minimum, reinoculation with different strains or species should be undertaken until this minimum is reached.

EDITOR'S ABSTRACT.

DRAINAGE OF CEREBROSPINAL FLUID IN THE TREATMENT OF ACUTE HEAD INJURIES. DELBERT H. WERDEN, Arch. Surg. **34**:424 (March) 1937.

Werden found in a study of a large series of cranial injuries that by far the most common lesion observed at operation was a subdural and subarachnoid accumulation of fluid. In most cases spinal drainage controlled the symptoms and signs of pressure. In a few others the patient responded well to surgical (subtemporal) drainage. Before operation the degree of pressure symptoms and consciousness was closely paralleled by the spinal fluid pressure. After operation continued coma and pressure signs were present in the majority of cases. These were markedly improved when intracranial pressure was controlled by further repeated spinal fluid drainage. Continued observation and accurate diagnosis of the intracranial lesion are essential in preoperative care in determining when surgical intervention is indicated. Spinal puncture is contraindicated in cases of extradural hematoma. Repeated drainage may predispose to increased secretion of cerebrospinal fluid and thus tend to sustain increased pressure.

GRANT, Philadelphia.

SURGICAL TREATMENT OF ANGINA PECTORIS AND RAYNAUD'S DISEASE. P. B. RANEY and K. H. ABBOTT, Bull. Los Angeles Neurol. Soc. **2**:66 (June) 1937.

According to Raney and Abbott, angina pectoris, in the absence of evidence of coronary disease, may be due to a disturbance in the pressor mechanism, especially in younger subjects. In such cases the condition is analogous to Raynaud's disease, and, as in the latter, prolonged vasoconstriction may lead to structural changes in the vessels. Operation on the postganglionic sympathetic nervous system relieves pain in angina of this type provided the sensory pathways are interrupted. Raney and Abbott cite recent work to show, however, that after interruption of the postganglionic neuron the vessels, after preliminary dilatation, acquire an intrinsic sensitivity to epinephrine. Thereafter any stimulus causing an increased secretion of epinephrine leads to further vascular spasm. Thus, the postganglionic neuron must be spared if coronary vasoconstriction is to be prevented.

Two cases are reported. The first was that of a woman aged 45, whose anginal attacks were precipitated by emotional stress and fatigue. The middle and inferior cardiac nerves were sectioned on the left side, and the sympathetic chain was removed from the middle cervical to the second thoracic ganglion, inclusive. The seizures ceased and had not recurred three months later.

The second case was that of a woman aged 42 with Raynaud's disease involving all the extremities and with scleroderma and trophic changes in the skin. During the attacks of vasoconstriction she also had epigastric and precordial pain. Eleven months after onset of the disease the thoracic portion of the sympathetic chain on both sides was sectioned below the third ganglion, and the rami communicantes to the second and third intercostal nerves were cut. Six weeks later bilateral lumbar sympathectomy was performed. All the symptoms ceased. The authors point out that in the second case postganglionic fibers were preserved, a fact which they think should insure permanent results. In conclusion, they state that they do not believe "that all patients with coronary disease have a primary disturbance in the sympathetic nervous system," nor do they "accept the theory that all patients with angina pectoris have primary disease of the coronary arteries." They think, however, that the symptomatic relief obtained in angina pectoris from cervicothoracic ganglionectomy is so strikingly successful that it should be employed in all cases in which the patient does not respond to medical treatment.

MACKAY, Chicago.

TREATMENT OF ALCOHOLIC PSYCHOSES WITH BENZEDRINE SULFATE: PRELIMINARY REPORT. E. C. REIFENSTEIN JR. and E. DAVIDOFF, J. A. M. A. **110**:1811 (May 28) 1938.

Reifenstein Jr. and Davidoff describe the results obtained in 28 patients who were admitted to the Syracuse Psychopathic Hospital in psychotic states brought on by alcohol. The patients were subjected to careful physical and mental observation and were then given from 10 to 30 mg. of benzedrine sulfate daily by mouth. In a few instances from 10 to 30 mg. of the drug was administered intravenously. In all cases the diagnosis was made according to the classification adopted by the American Psychiatric Association. Benzedrine sulfate produced a definite, and at times a marked, acceleration of improvement in 93 per cent of the patients. The drug appeared to be of most value in the conditions of recent onset, but exercised a favorable influence on alcoholic depressions in general. In states of intoxication brought on by alcohol in which no psychosis was demonstrable an even more satisfactory response to benzedrine sulfate was obtained. The depressive aftereffects of alcoholism were usually rapidly dissipated. The use of benzedrine sulfate in states of alcoholism with or without psychosis should be limited to institutionalized patients, in whom the dangers of habit formation with benzedrine sulfate itself and of harm from unpredictable untoward effects or serious toxic reactions can be adequately safeguarded. Under these conditions the drug may prove to be of value in overcoming chronic alcoholic habituation.

EDITOR'S ABSTRACT.

USE OF BENZEDRINE SULFATE IN POSTENCEPHALITIC PARKINSONISM. P. L. DAVIS and W. B. STEWART, J. A. M. A. **110**:1890 (June 4) 1938.

From the neurologic wards and the outpatient department of the Philadelphia General Hospital, Davis and Stewart chose 90 patients with parkinsonism for treatment with benzedrine sulfate. On only 74 of these patients were they able to complete their observations, owing to discharges, transfers and lack of cooperation. A preliminary clinical survey was made in each case, including a complete neurologic examination in which an attempt was made to record as accurately as possible the degree of severity of each manifestation of the disease. During the course of the treatment with benzedrine sulfate, the patients reported weekly on their subjective symptoms; observations as to any change in their physical status were noted, and frequent determinations of the blood pressure were made. At the end of the experimental period, in addition to a physical check-up, the subjects were asked to repeat the writing and copying tests; the strength of the grip was again tested, and motion pictures were taken of each patient. Two doses of benzedrine sulfate were given daily, the first at 8 a. m. and the second at noon. The age and systolic pressure of the patient were used as determining factors in prescribing the initial dose. Young persons with systolic pressures of 130 mm. of mercury or under were given doses of 60 mg. daily, 30 mg. at 8 a. m. and 30 mg. at noon. Persons with systolic pressures over 130 mm. of mercury and a few patients of advanced years were given only 40 mg. a day, and this dosage was maintained throughout the experiment. The previous regimen of the patient was not altered; the suitable dose of benzedrine sulfate was merely added. While 66 of the patients derived definite subjective benefit from the use of benzedrine, from the objective standpoint only 53 were improved. The most striking result was the effect on the oculogyric crises. Only 23 of the patients showed this symptom, and in every case the attacks were reduced either in frequency or in duration. However, in no case were they completely abolished. In 53 patients the strength of the grip was markedly increased, in some four or five times. There was a marked improvement in the ability to write and to draw on the part of 48 of the 63 patients who were able to write before treatment; of the 11 who were not able to copy even the square on the first trial, there were 3 who were

able to copy several of the figures while taking the drug. This improvement in writing and drawing is probably due to a general improvement in the extrapyramidal complex of symptoms and is a more accurate index of the degree of tremor, rigidity and loss of habit movements than are the usual methods of estimation. Tremor was noted in 66 patients and rigidity in 72. Tremor was reduced in 19 patients, unaffected in 40 and augmented in 7. Rigidity was decreased in 20 patients, unaffected in 46 and increased in 6. Of the 16 patients showing systolic blood pressures of over 130 mm. of mercury, the pressures were decreased in 10, unaltered in 3 and increased in 3. Of the 58 patients showing systolic blood pressures of less than 130 mm. of mercury, the pressures were decreased in 11, unaffected in 4, increased in 41 and of a vacillating type in 2. Benzedrine sulfate in the majority of patients with low blood pressure increased the tension from a moderate to a marked degree, whereas in patients under high tension the drug decreased the blood pressure below the previously recorded level. The latter effect of the drug, which is a vasopressor, seems paradoxic. The synergic effect of benzedrine in the atropine group was well brought out by the fact that 82 per cent of the patients receiving constant doses of the two drugs showed improvement, while only 64 per cent of the patients receiving benzedrine alone presented sufficient objective evidence of benefit to be classed as improved.

EDITOR'S ABSTRACT.

INSULIN SHOCK THERAPY OF SCHIZOPHRENIA. E. K. KRASNUSHKIN and G. M. KHANLARYAN, Sovet. psikhonevrol. **13**:5, 1937.

Krasnushkin and Khanlaryan point out certain antagonisms between schizophrenia and a number of diseases and pathogenic factors. There is some antagonism between acute infectious diseases and schizophrenia, and, on the other hand, a tendency to symbiosis with chronic diseases exists. A pyknic-thymic constitution exhibits an antagonism toward schizophrenia, but the shock-producing factors manifest this antagonism in the highest degree. Among these, the authors mention physical trauma to the brain, epileptic attacks, strangulation, psychic shock and the agonal state. The convulsion therapy of Meduna and the insulin therapy of Sakel utilize these antagonistic shock-producing agents, the first by provoking epileptic attacks with the aid of camphor or metrazol and the second by inducing hypoglycemic shock. The glycopenic states in schizophrenic patients are complicated by certain peculiar psychotic manifestations, which in themselves are of favorable prognostic significance. Among these are a sense of euphoria, syntonia, self-analysis and criticism and the disappearance of the constant schizophrenic symptoms. Among other manifestations are motor stimulations, maniacal states, occasionally depressive and hysterical states and exacerbations of schizophrenic symptoms. According to the authors, these manifestations, without actually reaching a comatose or precomatose state, give a favorable prognosis.

The authors have treated 52 patients by the insulin shock method, most of them with early stages of the disease, up to one and one-half years in duration, and have noted a high percentage of recoveries and remissions, particularly in the early forms. The most striking results were obtained in paranoid types. The authors observed in most of their patients the development of prolonged (several weeks) hypomaniacal states as a transitional phase toward a favorable remission. The patients, at the same time, manifested improvement in the physical state and a shift toward the physical characteristics of the pyknic constitution. With the aid of orthocardiographic studies, Dr. Lakosin demonstrated a change from the vertical position of the heart, characteristic of schizophrenia, to the dorsal position, characteristic of a pyknic constitution. The authors believe that the effective action of insulin therapy is due to two antagonistic factors: (1) the shock induced by glycopenic attacks, resembling those of epilepsy, which is accompanied by anoxemia of the brain cells, as in strangulation, and induces in its deep states coma nearing the agonal state, and (2) stimulation of elements antagonistic to the circular con-

stitution, a fact which explains the greater number of remissions in paranoid types, since these exhibit more ingredients of that constitution than do other forms of schizophrenia.

EDITOR'S ABSTRACT.

Special Senses

COMPRESSION OF CHIASMA, OPTIC NERVES and OPTIC TRACTS BY INTRACRANIAL ANEURYSMS. G. JEFFERSON, Brain **60**:444 (Dec.) 1937.

According to the clinical classification of Bramwell, intracranial aneurysms may present themselves as apoplectic and paralytic. It is with the latter only that Jefferson deals, and of these only with such as have affected the visual apparatus, that is, by compression of the optic tract, chiasm or optic nerve. Of 53 cases of intracranial aneurysms, 16 were pure subarachnoid hemorrhage (with nothing to indicate the precise site of the aneurysm); 9 were associated with paralysis of cranial nerves (usually the third); 16 were saccular (nonfistulous) aneurysms of the internal carotid artery in the cavernous sinus, and 12 were basal aneurysms with disturbance of the visual pathways. The last 12 cases are reported after the aneurysms were grouped under four headings: (1) those interfering with the optic radiation and striate cortex, 3 cases; (2) those compressing the optic tract, 1 case; (3) those affecting the optic nerves, 2 cases, and (4) those involving the chiasm, 6 cases. Of the first group the sudden onset of the disorder and the nonprogressive nature of the clinical picture leave no doubt that 2 were examples of thrombosis of the posterior cerebral artery and the third was an instance of thrombosis of some part of the middle cerebral artery. In all these cases the immediate clinical picture was that of subarachnoid hemorrhage. The pathologic features of the type of aneurysms under discussion seem in no way to differ from that of the so-called berry aneurysm. In general they occur, like other aneurysms, at the bifurcation of a large vessel, in this case the internal carotid artery, perhaps where the ophthalmic artery leaves it or, in the suprachiasmal group, at the point where the anterior cerebral artery is joined by the anterior communicating branch. The differential diagnosis of a chiasmal lesion rests on the nature of the field defect, together with the manner of its evolution and the rapidity of its development, the degree of pain associated with the evolution of the visual defect, the coexistence of other neurologic signs, the presence or absence of tuberal or endocrine disturbance and the roentgenographic evidence. There is only one useful treatment in these cases, and that is ligation of the carotid artery.

EDITOR'S ABSTRACT.

NUTRITIONAL RETROBULBAR NEURITIS FOLLOWED BY PARTIAL OPTIC ATROPHY. D. FITZGERALD MOORE, Lancet **1**:1225 (May 22) 1937.

The retrobulbar neuritis described by Moore occurred in Nigeria, Africa. Similar conditions have been reported on the Gold Coast and in Sierra Leone, Africa, and in Jamaica, the Solomon Islands, Barbados and the Malay Peninsula. The history of patients with this condition is definite. Vision becomes suddenly misty, and there is difficulty in seeing clearly at a distance and in reading print. There is photophobia in bright light. The patient invariably has, or has had, one or more attacks of sore tongue. There are white patches at the edges of the lips, and the scrotum is dry, scaly and itchy. The cutaneous lesions vary in intensity; usually the tongue looks raw, and the edges of the lips are only slightly cracked, the genital skin being smooth and dry. In school children these lesions frequently pass unnoticed, and their cause is not recognized, particularly as they tend to improve in holiday time—that is, on return to natural home conditions. Examination of the eyes reveals no external changes. In the early stages there are few or no alterations in the fundus, but definite changes appear later, usually about two months after the onset. After the first symptoms there is definite pallor of the disks, more extreme on the temporal side; in severer and more advanced

stages the disks appear to be typical of primary atrophy of the optic nerve—almost dead white, with thin vessels and grayish retinas. Some very severe forms may also show true optic neuritis with postneuritic changes. The effect on vision is profound and may be permanent if the condition is untreated.

The disease itself is curable with marmite (an antineuritic vitamin preparation) alone or with yeast alone; the lesions of the skin are curable with autoclaved products, and the lesions of the eye are probably curable with such products. The experiments of Landor and Pallister definitely established that the lesions of the skin and mouth are dramatically amenable to vitamin B_1 therapy. Cod liver oil and fruit juice had no effect on the lesions. Moore obtained excellent ophthalmologic response in early stages up to six months, but conditions of more than one year's duration responded less well. More than 200 selected patients were treated for periods up to ten months with yeast or marmite alone. All the lesions of the skin cleared up rapidly, and the visual response was good in early stages. Eight patients, especially selected for the cutaneous lesions, were treated with autoclaved, dried yeast, with good results. From his own work, Moore has not proved therapeutically that the ophthalmologic response is due to vitamin B treatment exclusively, but other general evidence is so strong that he believes that this only awaits confirmation.

WATTS, Washington, D. C.

CURIOUS OCULOVESTIBULAR DISTURBANCES IN A CASE OF DEEP TEMPOROPARIETAL TUMOR. J. A. BARRÉ and CORINO D'ANDRADE, Rev. neurol. **67**:497, 1937.

Barré and d'Andrade report the case of a man aged 37 with a history of headache for five months, fits of unconsciousness with falling to the right, ataxic gait, astasia, bilateral papilledema and blindness and exceedingly hyperactive nystagmus to the caloric test on the left side. The nystagmus persisted for over five minutes. On the right side the same test gave an immediate, but slow. nystagmus of slight amplitude, lasting for over four minutes, with no vertigo. The tumor was in the right parietal lobe. This prolonged caloric nystagmus has so far been observed in only two types of conditions: lesions of the tegmentum of the midbrain and tumors of the parietal lobe. In cases of lesions of the midbrain oculomotor disturbances are present. The parietal tumors may produce this syndrome by compressing the midbrain.

LIBER, New York.

VESTIBULAR DISORDERS IN THE POSTCONCUSSIONAL SYNDROME. G. PORTMANN and J. DESPONS, Rev. d'oto-neuro-opht. **15**:674 (Dec.) 1937.

Thirty-six patients are included in this study of the condition of the vestibular apparatus. All had closed cranial traumatism. Twenty of the patients had tinnitus and deafness; 2 suffered from tinnitus without vertigo as a result of electric shock while using the telephone. Vertigo was an especially prominent symptom. Only 10 of the 36 patients had spontaneous nystagmus, which was modified by change in position of the head.

The labyrinthrine tests showed that twenty patients had labyrinthine hyperexcitability; in 9 the reactions were normal, and in 7 there was hypoexcitability. In 6 of the 20 patients the hyperexcitability was noted only with the caloric test. Hypoexcitability in patients with concussion indicates peripheral labyrinthine involvement; most of them have also involvement of the cochleas. While tinnitus is often observed, deafness is less frequently found. Therefore, in most cases of concussion the vestibular disorders are of central origin. This is attested also by the type of spontaneous nystagmus, the variability of the reactions, the dissociations, the disharmony of the nystagmic responses and the reactional movements and the importance of the psychic factors observed. The vestibular disorders in cases of injuries to the head can be understood only if they are placed in the frame of other clinical manifestations of the postconcussional syndrome.

DENNIS, San Diego, Calif.

VESTIBULOVEGETATIVE REFLEXES IN MAN. G. MARINESCO, S. DRAGANESCO, A. KREINDLER and A. BRUCH, Rev. d'oto-neuro-opht. **15**:690 (Dec.) 1937.

Vegetative manifestations (vertigo, nausea, vomiting and pallor) accompanying stimulation of the vestibular apparatus are well known. The proximity of the central vestibular centers to the pneumogastric nuclei and the vegetative neurons in the reticulated substance of the bulboprotuberential region permits the assumption of a close functional correlation. The physiologic mechanism of these manifestations was studied by Marinesco, Draganesco, Kreindler and Bruch, who named them vestibulovegetative reflexes. The following vegetative reactions to irrigation of the ear were observed in man: 1. At the moment of appearance of nystagmus the pulse rate diminished by from 8 to 10 beats and was accelerated toward the end of the period of irrigation. 2. Maximal arterial tension diminished. 3. The oscillometric index increased in certain cases. 4. The subungual capillaries were constricted when nystagmus appeared. 5. Important plethysmographic changes occurred. Maximal vasomotor constriction occurred with the appearance of nystagmus. Vasodilatation, which persisted after cessation of irrigation, followed. There appeared to be a correlation between this dilatation and the vegetative phenomena. 6. Respiration became more ample with diminution in frequency at times.

In cases of multiple sclerosis, after irrigation of the ear with cold water, vasodilatation alternating with vasoconstriction was marked and persisted for a long time after cessation of the irrigation. The vestibulovegetative, especially the vestibulovasomotor, reflexes were lively. It is well known that vegetative disturbances associated with labyrinthine troubles are frequent in cases of multiple sclerosis; the bulbar lesions involve the floor of the fourth ventricle, which explains these manifestations. In cases of postencephalitic parkinsonism in which there had not been treatment with alkaloids the vestibulovasomotor reflexes were feeble or absent; rendering the vagus nerve less excitable by the use of atropine caused these reflexes to reappear. In a case of causalgia of the left ulnar nerve only insignificant vasodilatation was produced by labyrinthine excitation. A similar result was observed in a case in which cervical sympathectomy had been performed bilaterally. In 2 cases of hysteria irrigation of the ears caused intense vasoconstriction, followed by marked vasodilatation. In a case of alcoholism, complicated by vertigo, intense and lasting vasoconstriction persisted, even after the irrigation was stopped, and was followed by tardy and prolonged vasodilatation.

Kreindler determined that the chronaxia of the sensation of vertigo was from four to nine thousandths of a second when the vestibular nerve was excited by closure of the continuous current. Marinesco and Kreindler determined the chronaxia of the vestibulovasomotor reflex, using a current of from 3 to 6 milliamperes. The chronaxia of this reflex was almost equal to that of the vestibulospinal reflex, oscillating between nine-tenths and one and seven-tenths thousandths of a second. The time of summation, however, was from four to five seconds instead of from two to three seconds, as for the vestibulospinal reflex. There was isochronism between the centripetal arc (nervus vestibularis) and the centrifugal arc (nervus vagus) of the vestibulomotor reflex.

The excitability of the vestibular apparatus was examined with this method in cases of neuroma of the acoustic nerve, multiple sclerosis, epilepsy, parkinsonism and Ménière's disease. In the cases of neuroma the chronaxias of the acoustic nerve and the vestibulospinal and vestibulovegetative reflexes were increased, indicating a pathologic change in the centripetal arc. The time of summation for the vestibulospinal and vestibulovegetative reflexes was normal, which indicated normal excitability of the bulbar centers of the vestibular apparatus. In 3 cases of multiple sclerosis the chronaxia of the centripetal arc (vestibular nerve) was normal, but the time of summation was increased, indicating disturbance of excitability of the bulbar centers. In cases of epilepsy chronaxia of the vestibular nerve and the time of summation were increased. These observations are probably related to the fact that in epilepsy the reflexes of the carotid sinus are diminished. Pistocchi's

experiments showed that denervation of the carotid sinus causes increase in the chronaxia of certain neurons, probably from elevation of the normal heterochronisms of the synapses.

In cases of parkinsonism the results varied but in general the chronaxia of the vestibular nerve was normal and the time of summation modified. In 1 case chronaxias of the vestibular nerve and of the sensation of vertigo were increased. With iterative excitation, the chronaxia of the vestibular nerve was little changed, but the time of summation was diminished for the vestibulovegetative reflex and increased for the vestibulospinal reflex. These facts indicate that in parkinsonism the disturbances of excitability affect especially the central neurons. In 3 cases of Ménière's vertigo there was disturbance of pathways for the vestibulovegetative reflexes; the vestibulospinal reflexes were normal.

The afferent pathway of the vestibulovegetative reflex is the cochleovestibular nerve; in the bulb are functional connections between the vestibular nuclei and the vagosympathetic centers; the efferent pathway is the vagosympathetic nerves. The mechanism of these vasomotor modifications is not abdominal vasodilatation but direct action on the peripheral vasomotor nerves. The labyrinthine apparatus exercises a reflex action on both the central and the peripheral vasomotor nerves, as shown by the authors (*Rev. d'oto-neuro-opht.* **1**:188 [March] 1934). Aronson's experiments showed that each labyrinth has cortical representations in each cerebral hemisphere. The pathway of conduction is by way of both the posterior longitudinal bundle and the tractus vestibulomesencephalicus and perhaps makes use also of the two cerebellar hemispheres, and even of the cochlear pathway. Thus, the labyrinthine apparatus is deeply integrated in the complex of the vegetative system and in the cortical motor mechanism. In order to comprehend the role of the labyrinthine apparatus, it is necessary to consider not only the vestibulokinetic (nystagmus) and vestibulotonic (deviation and disequilibrium) reflexes but also the vestibulovegetative reflexes.

DENNIS, San Diego, Calif.

CROSSED VESTIBULAR DYSREFLEXIA IN THE COURSE OF A SYNDROME OF THE PONTILE TEGMENTUM. H. GIROIRE and A. CHARBONNEL, Rev. d'oto-neuro-opht. **15**: 710 (Dec.) 1937.

Giroire and Charbonnel report the case of a man aged 60 who had paralysis of the right side of the face and a sensory hemisyndrome of the syringomyelic type of dissociation on the left, accompanied by disturbances of cerebellar origin on the right side and of pyramidal origin on the left. There were no symptoms of vestibular involvement. The diagnosis of a small softening, localized at the level of the pontile tegmentum on the right, near the facial nucleus, was made. Vestibular examination with the caloric rotation and galvanic tests, which normally cause nystagmus to the right and deviations to the left, gave normal responses. No nystagmus to the left and no deviations to the right were elicted by any of the tests. This labyrinthine formula corresponds exactly with that in the 2 cases reported by Barré and Charbonnel, which they called "crossed vestibular dysreflexia." Barré proposed the name *hémiavestibulie latérale homonyme* for the syndrome, which indicates a central lesion of the vestibular tracts.

DENNIS, San Diego, Calif.

A SPECIAL FORM OF DEVIATION OF THE EYES ASSOCIATED WITH HEMORRHAGE OF THE PONS. A. BIEMOND, Psychiat. en neurol. bl. **41**:349, 1937.

The old doctrine that patients with cerebral hemorrhage have conjugate deviation of the eyeballs toward the side of the lesion while those with pontile hemorrhages have deviation away from the side of the lesion is only partially true. In 4 patients with cerebellar hemorrhage and in 2 with a pontile hemorrhage no deviation of the eyeballs was observed; of 24 patients with a cerebral hemorrhage

not more than 12 had a typical deviation, while 2 showed deviation away from the side of the lesion. In 2 patients with a fresh pontile hemorrhage a peculiar, as yet undescribed, position of the eyeballs was observed. In both these patients the bulbs were rotated downward and showed slow rhythmic movements in the lateroinferior direction. The movement was stronger in the left eye; occasionally this eye showed a rotatory movement to the right side. This form of deviation was of short duration. Biemond assumes that it was due to an excitatory state of both trochlear nerves.

LEWY, Philadelphia.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

TRACY J. PUTNAM, M.D., *Presiding*

Regular Meeting, May 19, 1938

INTRACRANIAL ANEURYSMS. DR. CHARLES A. MCDONALD and MILTON KORB, Providence, R. I.

A report of 2 cases of intracranial aneurysm is presented, including observations on brains prepared by the Rosett bakelite method. The first patient, aged 37, had a ruptured aneurysm of the internal carotid artery, which had burst in and around the right third cranial nerve. The second patient, aged 24, showed a ruptured aneurysm of the basilar artery. There were syphilitic aortitis, extensive arteriosclerosis of the cerebral arteries and an anomaly of the circle of Willis consisting of the absence of a communication between the basilar and the left posterior communicating artery.

In a review of the literature, 1,125 cases were collected, which were analyzed according to the frequency of involvement of the artery, the age incidence and the condition of the arteries.

A bibliography is presented for reference which contains the cases reported in the literature arranged in chronologic order, the location of the aneurysm, the age of the patient, the condition of the arteries, when stated, the author and the reference.

THE VASCULAR SYSTEM OF THE SPINAL CORD IN MAN. DRS. T. H. SUH and LEO ALEXANDER, Worcester, Mass.

This article will appear in full in a later issue of the ARCHIVES.

METHOD OF MEASURING CONSCIOUSNESS IN ATTACKS OF PETIT MAL EPILEPSY. DR. ROBERT S. SCHWAB.

Since the work of Gibbs and Lennox on the study of convulsive disorders by means of the electroencephalogram, there is little doubt that there exist short, mild petit mal attacks unknown to the patient and not noticeable to the observer. These larval attacks, as Gibbs aptly termed them, have a characteristic pattern in the electroencephalogram that sharply differentiates them from the normal brain rhythm and from the fast potentials found in grand mal attacks or in cortical disturbances associated with organic lesions, such as tumor or pressure. The high voltage slow wave followed by a sharp spike repeating itself for from one to thirty seconds is one of the most striking electroencephalographic findings. Gibbs has observed that patients may continue counting even when the characteristic attack occurs.

The question of what happens to consciousness during the fraction of a minute of the larval attack is important in evaluating the seriousness of the cortical disturbance and its influence on other cerebral activity. Counting numbers does not lend itself to quantitative measurements and may be more automatic than conscious.

The following method was used in 14 cases in which larval petit mal attacks were shown. The apparatus is simple to connect with the electroencephalographic

apparatus and is easy to build, and there is a minimum of technical complications in its operation.

The signal pen is connected by means of a double pole, single throw spring switch to one arm of the switch, and an electric light circuit, to the other. Thus, when the switch is closed the pen indicates the exact instant that the light goes on. The signal pen circuit also runs through a mercury contact that can be opened by inflating a tambour with a rubber bulb, allowing the pen to fall back to its original position. The rubber bulb is placed in the patient's hand. It is firm enough to require deliberate flexion of the fist before it actuates the tambour; copper tubing ⅛ inch (32 mm.) in diameter, and pressure tubing complete the connection between the bulb and the tambour.

The patient is instructed to squeeze the bulb the moment he sees the light, which is a 150 watt bulb hung 3 feet (90 cm.) over his head and bright enough

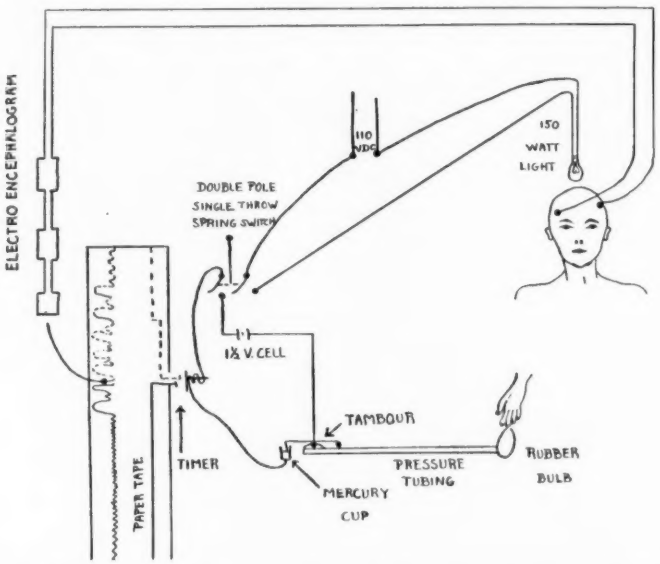


Fig. 1.—Diagram showing connections of the reaction time apparatus with the electroencephalographic apparatus.

to be perceived even when the eyes are closed. The patient is in the dark until the light goes on.

Thus, when the light goes on the signal pen moves to the side of the paper tape, and as soon as the patient squeezes the bulb the pen falls back.

The interval is measured along the tape and represents the reaction time to this visual stimulus. In 100 normal persons it was about 0.25 second, varying from 0.3 to 0.2 second. When a patient suspected of having petit mal attacks is observed, several reaction times are obtained to find his normal. Then, either the patient hyperventilates or, if he is having spontaneous attacks the observer waits until a seizure occurs. The observer has the knife switch in his hand, and as soon as he sees the characteristic wave spikes he throws the switch. If the patient is conscious the reaction time is normal or slightly increased. If he is unconscious no response occurs until the attack is over or consciousness returns.

If consciousness is impaired but not lost, the reaction time will be doubled, or even tripled.

The procedure is so simple that it can be repeated a number of times, with or without hyperventilation while taking or not taking phenobarbital, when reclining or sitting and under other conditions.

I have found that in some cases consciousness is never lost. In others it is always lost. In some it is lost during some of the attacks and preserved in others. The longer attacks seem generally to be associated with loss of consciousness.

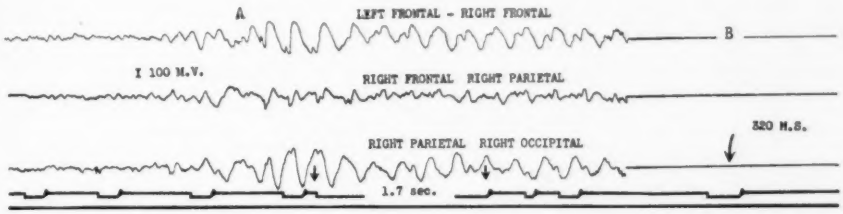


Fig. 2.—*A*, reaction time taken during a petit mal attack of five seconds' duration, showing prolongation of one and seven-tenths seconds. The reaction time is indicated between the two arrows. *B*, normal reaction time (320 milliseconds) for the same patient taken after the experiment.

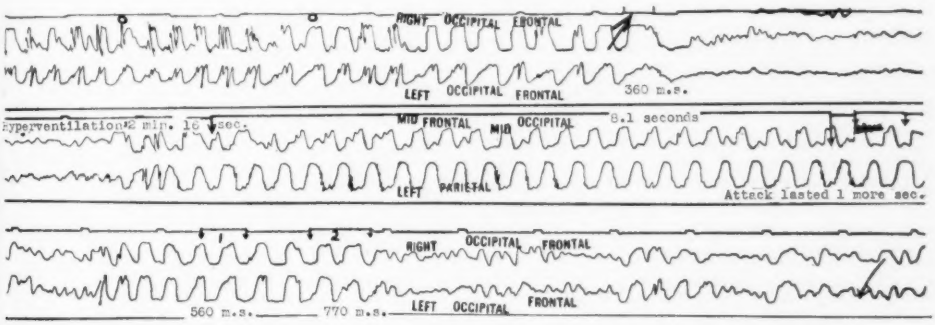


Fig. 3.—Record at top: Three measurements of the reaction time during a petit mal attack of fifteen seconds' duration. The first two marks for reaction time were *O*, indicating that there was no response and that the patient was unconscious during both these periods. The third reaction time, marked with the black arrow, was approximately normal and occurred at the end of the attack.

Second line: Reaction time during an attack of petit mal epilepsy, with no response to the signal until eight and one-tenth seconds elapsed, showing a long period of unconsciousness.

Third line: Tracing showing slight prolongation of two reaction times during a petit mal attack.

It is possible to use the stimulus several times in one attack. The benefit of anticonvulsant drugs can be quantitatively measured by this means.

PSYCHIATRIC MANIFESTATIONS OF MUCOUS COLITIS: REPORT OF A CASE. DR. MORRIS YORSHIS, Worcester, Mass.

Reactions involving tension are characterized by minor anxiety symptoms which develop under strain, especially in response to frustration. Every person has a constitutional expression of tension. To this broad group of symptoms belong complaints of various types of headache, indigestion and diarrhea, occurring singly or in combination. Study of the setting and personality, with a review of the life development, leads to a correct understanding of the disturbance and reveals opportunity for correction. An account of a patient who was troubled with colitis for one year follows.

REPORT OF CASE

History.—A woman aged 28, single, a brunette, 5 feet and 7 inches (170 cm.) tall and weighing 147 pounds (66.7 Kg.), was the youngest sibling in a family of five. She was dressed in masculine style and was low busted.

In December 1935, after a Pott's fracture of the left ankle, the patient had difficulty with the bowels. When she returned to work in January 1936 she had diarrhea and pain and passed blood and mucus almost continually, so that she was in bed from time to time and had to have iron and careful dietary management. In May 1936 she was taken to a hospital because of symptoms of proctitis, which had become so troublesome that she could not go out in the community socially because of explosive bowel movements without warning. Roentgenographic examination showed "a spastic state" in the lower portion of the intestinal tract, and proctoscopy revealed marked irritation of the mucous membrane at the lowermost portion of the rectum; the latter responded to treatment with simple suppositories. Throughout the course of the trouble there was the strong impression that it was of a functional nature, but it seemed only intelligent to track down any possible organic disease before trying psychotherapy or in any way drawing the patient's attention to her emotional life. During the summer of 1936 she was well, with gradual subsidence of symptoms; so it seemed obvious when, on her return in September 1936, she returned to her former symptoms that the aid of a psychiatrist should be sought.

Family History.—Her account of her family background follows. Father: He was the youngest in his family. "I never knew he liked me when I was small. He dropped me once, and I got a scar on my lip. He is my father, and that is all I could say." He never was a good provider, had little education, was set in his ideas and moody, had no inner resources and was always the "home type." "I would shake hands with my father, but would kiss my brother."

"He's hard of hearing. After my mother died, in November 1935, he insisted on unburdening himself to me, and I dreaded to go home. When he had a shock in April 1935, I was the only one that could take care of him. He's just like a puppy with me."

Mother: The mother graduated from high school and married at the age of 20. "She was the boss of the family." "I could never talk to her about intimate things; she was nervous and had stomach trouble. She was part of us. She always discouraged me. My mother's death did not affect me greatly. She died of Bright's disease."

Maternal Grandmother: "A straight-laced New Englander. She is 96 and lives on her interest, and yet was always afraid that she was going to the poor house. She's deaf. She has a cast iron stomach."

Brother Henry: He was 20 years the patient's senior. "He put himself through school, took the place of my father and always gave me a push. He is terribly nervous and suffers from indigestion. He got married when he could afford it. He raised a family when he could afford to."

Only Sister: She was 18 years older than the patient. She did not learn easily. "She hated my father. She was narrow minded, nervous and excitable. She had to run off and get married. She died on Nov. 11, 1936."

Second Brother: He was 14 years older than the patient, "crude and just like my father. He has an ulcer of the stomach and has to be careful of his diet."

Youngest Brother: He was 4 years older than the patient. "We were always together. I played with his boy friends. When my mother died it took a lot out of him. He is a regular old lady. He flares up like my father. He does not initiate by himself. He was the object of jealousy of my father. He's masculine, is 6 feet and 1 inch (185 cm.) tall and has curly hair; he is not too interested in girls."

Chronologic History.—The patient was born on Sept. 26, 1910, a menopausal child and the youngest sibling. The chronologic sequence of certain facts is given in the accompanying tabulation.

Date	Events	Age, Yr.	Comment
1912	.....	2	A tomboy; played with youngest brother and his chums
1913	.....	3	
1914	Some sex experience with brother Francis.....	4	
1915	Sex assaults by boy.....	5	
1916	Departure of sister; elopement; forced (?) marriage; abortion	6	From age of 6 to 18, lived on and off with oldest brother; cursed and was mean in relation to sex only; endured petting parties, but would get "sick to her stomach"
1918	Slept with brother off and on.....	8	
1919	Mutual masturbation with older girl.....	9	
1923	Brother had sex relations with chum of patient; patient heard this, was upset and depressed; her brother became repulsive; she cried a great deal; felt lifeless; thought she was not liked; did not think that such a thing would be done by her brother; felt sorry for herself; had colitis for four weeks; did not tell doctor she passed blood with onset of colitis; no depression. Menses started	13	
1924	.....	14	Arm's length attitude toward sex
1927	Graduated from high school.....	17	
1928	Postgraduate course for three months.....	18	
1929	Lived with sister-in-law; special course at trade school; worked for one year; niece born	19	
1930	Attended school in Boston to become a dietitian	20	
1931	First job; sexual assault by "nigger" or Spaniard; considerable attention; homosexual assaults at the seminary; faculty insinuations: "What, no students with you!"	21	
1932	.....	22	Attitude to employer (1) She was deaf and (2) disagreeable
1933	Appendectomy	23	(3) Stomach turned over at the sight of her (4) Called her "senile paranoid"
1934	Considerable attention by a young man who was just a "pal"	24	(5) "She called me 'Alibi Pete'"
1935	July: Met Henry, twin brother of a youngest sibling, her second cook at the campus; he was very attentive October: Henry departed; patient depressed, cried a great deal. "I was down in the dumps, nervous. I was sick of living, sick of everybody; sleepless; lost weight; acted crazy. I didn't care whether school kept or not." Missed the attention; blamed job November 29: Death of mother December 1: Funeral; few stomach rumblings December 4: Broke her ankle December 19: Passed blood; colitis; depression lifted. "She has the colitis to worry about."	25	(6) She did a lot for me
1936	Colitis off and on; worse when she was angry and irritable, when her father visited her and when she went home November 11: Sister died December: Resigned	26	

Personality.—This was characterized by tremendous ambivalence, feelings of inferiority and fluctuating moods.

"I don't care to be done; I know I'm soft and suspicious. I wish I were a man. I have moments with every one. You can tell when I come in whether I am one way or the other. I am self conscious. It is easier for me to follow the mob than to assert myself. I criticize others for doing things I do myself. I'm not tolerant. I don't seem to have any feeling for anybody. My sister's and my mother's death did not seem to affect me greatly. I am like my father because I get suggestions from the outside. I am more of a war horse. I always go out with a bunch of women. I am fussy about food. It has to look well. I am game during emergencies, but go to pieces afterwards. I never get any sympathy. If people ever say something that I don't like, my stomach turns over. It does a somersault. I underestimate myself rather than stand up. I sit back, get paralyzed and look as if I haven't a brain in my head when I go out to get a job. The people I pal with are aggressive, as I would like to be. I have no friends at home. I used to debate the issue in my own mind about going home because there was nothing constructive there. It was all a feeling of duty. I would go into the house full of pep, but I was glad when I could get away. My ambition was to give my mother all the things she never had at home, but I never reached that point. With superiors I get tongue tied; I don't relax. I am very sensitive, especially to other people's attitudes. I like to be liked. I'm an egotist. I can never break down the barriers. A teacher is always a teacher to me. I am overmodest. I am not very good at sizing people up. I don't like people with an inferiority complex. I am never at ease. I don't seem to be able to initiate on my own. I often get depressed and wish that I were elsewhere. I used to read a lot, but I haven't read a book for a long time. My mind is at rest when I am busy. Any one who has any authority frightens me, even if I get to know them. I wait for suggestions. My sister-in-law suggested that I take up food work. My roommate suggested that I learn to use the typewriter. I shall probably end by washing dishes in the Waldorf restaurant. I have never known the feeling of doing as I please and never had the feeling of being independent. I never seemed to know where I stand, with my father, sister-in-law and employers. I am never quite sure of myself. I wish I had more spunk. I never did things on my own; everybody tells me that I look as though I had all the confidence in the world, but I feel 'quakey' in my boots. I never tried real hard to do things. I was easily influenced. I can't understand how my sister ever got enough spunk to get off and elope. I feel as if I doubt my own self. Sometimes I feel as if there was no place for me." She dreamed that she saw a mother rat and four little mice, round and fat, in her stocking. "I yelled. Out of the heel came another; he just came up late." "I get kind of nervous about having a career. I don't know whether I have any ambition or not. I always do the stereotyped thing. I have always been told that I had an orderly mind, but I learned this from my sister-in-law. The girls tell me that I keep things too clean. I can't stand children, especially so since niece was born. I do a lot of day-dreaming. I did a lot of things in my imagination. All the things I don't have the courage to do, I visualize myself as doing." She dreamed about being kissed by a monk, being bent backward by a boy and being caressed by a doctor. "I always learned that I am supposed to be good and act my age. I had to be old maidish. I grew up in a hurry and never took criticism well. I am loyal. If things don't go through I would get nervous and panicky. I just had the feeling I couldn't breathe. Sometimes I would have to go to the 'John' anywhere from one to ten times a day. It seemed as though my heart was in my throat. I dislike a moody person. Some people tell me I am too serious. My moods come out of a clear sky. When I am in the dumps I am sick to my stomach."

Ideas in Relation to the Oral, Pharyngeal, Laryngeal and Gastrointestinal Tracts.—"The only time I was dropped was by my father, I bit my tooth through my lip, and I work on it all the time." The patient often went over to a

neighbor for a second breakfast. "Cravings mean to me nothing but food"; she chewed gum just to keep her jaws moving. "I talk too much; the family thought I ought to be on the stage as an impersonator because of the noises I could make with my mouth. Everybody in the family has a nice voice. I like to sing. I would yell and shriek just for entertainment when at stool. I have had nervous spasms in my throat when I couldn't swallow. I've had lumps in my throat and couldn't get anything down. I'd like to take a chunk out of something or some one. Sometimes I would feel my intestines knotted, as if they were going to turn over. When I was sick to my stomach the doctor thought I had gallbladder trouble, and I've had my appendix out. My father insisted on having the toilet seat brown when I was painting the bathroom."

Etiologic Factors.—The following factors may have had an etiologic role in the disturbance: (1) the gastric complaints of the mother and two siblings, particularly the oldest brother, who the patient felt treated her like a father; (2) preponderance of the patient's complaints in relation to the oral-anal tract (lips, noises, swallowing, breathing, digestion, pains and diarrhea); (3) apparent rejection by the father and domination by the mother; (4) rejection by the brother when he had sex relations with the patient's girl friend, apparently evoking a depression first, followed by colitis and then menstruation; (5) birth of a female child, the patient's niece, replacing the patient as the only child in the brother's household; (6) recognition that the father was like the grandmother, employer and sister-in-law in respect to defects in hearing and that she did not know where she stood with any of them; and (7) rejection by her boy friend.

Comment.—The two clearcut attacks of depression followed by colitis had a common element. In both instances the apparent cause was the rejection by the brother or his substitute. To use the patient's own terms: "We all get sick to our stomach, and this is the only way I could get rid of it." Her love and hate for her father and brother and her desire to take revenge for the rejection were expressed through the gastrointestinal tract. She rationalized by believing that her difficulties were due to her job, and since her resignation has had no recurrence of symptoms.

Book Reviews

Les inégalités pupillaires d'origine sympathique dans les lésions du système nerveux central. By Marcel Kipfer. Price, 25 francs. Pp. 182. Paris: Librairie Louis Arnette, 1938.

In this monograph the author has collected material from both clinical and experimental literature which indicates that lesions in descending cervical sympathetic pathways cause a typical Horner's syndrome on the side of the lesion. These interruptions may occur in the peripheral sympathetic chain, the spinal cord, the brain stem or the hypothalamus, or even in the thalamus. To investigate the last, which heretofore has been seen only in clinical cases, the author placed electrolytic lesions in the diencephalon of dogs. Thirty-one operations were performed, and 3 are reported on. In 2 dogs a typical Horner's syndrome, with miosis, exophthalmos and narrowing of the palpebral fissure, was transiently obtained. The lesions were in the anterior and superior part of the thalamus. In the third animal, with a lesion in the external thalamic nucleus, only homolateral miosis was obtained. The author used the reactions of the pupil to cocaine and atropine to prove that the pupillary inequality was due to lack of sympathetic tone. However, the data submitted could also argue for interference with oculomotor inhibition, which has been shown by Ranson, F. H. Lewy and Bremer to be obtainable by intracerebral stimulation of thalamic and hypothalamic regions. The question presents itself whether the diencephalic neurons normally responsible for the tonic sympathetic innervation of the pupil and orbital smooth muscle should be considered as representatives of the sympathetic system *per se* or as secondary sensory afferent and internuncial neurons on the activity of which some forms of autonomic tonus are normally dependent. The author has presented much suggestive material, which, as he admits, demands further investigation. The monograph contains 182 pages, of which 7 are devoted to original experiments.

Einführung in die Ventrikulographie. By Benno Schlesinger. Price, 20 marks. Pp. 246, with 146 illustrations. Berlin: Urban & Schwarzenberg, 1937.

This monograph is an excellent and comprehensive review of the principles of roentgenographic interpretation of ventriculographic plates. The text occupies a large part, and there are a few reproductions of actual photographs. In the main, however, the illustrations are diagrammatic and have been done well enough to suit the purpose.

La hernie postérieure du ménisque intervertébral. By Pierre Glorieux. Price, 40 francs. Pp. 102, with 98 illustrations. Paris: Masson & Cie, 1937.

This monograph is a general review of a subject of much recent interest. There are numerous and excellent illustrations and diagrams, and the material is well covered in much the same manner as has been done in frequent reviews written in this country.

CORRECTION

In the article by Dr. George B. Hassin entitled "Disseminated Encephalomyelitis (Meningoencephalomyeloradiculitis) Versus Multiple Sclerosis," in the December issue (ARCH. NEUROL. & PSYCHIAT. **40**:1111, 1938), "cell-containing methods" in the eighth line from the bottom on page 1115 should read "cell-staining methods," and "nasal ganglia" in the first line on page 1121 should read "basal ganglia."